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A COMPARISON OF THE CHANGES IN THE HUMAN ELECTROCARDIOGRAM FOLLOWING THE ADMINISTRATION OF STROPHANTHIN AND ACETYLCHOLINE AND DURING VAGAL STIMULATION*†

NIELS A. NIELSEN, M.D., AND MOGENS TRIER, M.D.
COPENHAGEN, DENMARK

IN A previous work it was shown that the cardio-inhibitory vagal effect caused by the digitalis substances is most likely due solely to a sensitization of the heart muscle to the normal vagus tone (Abdon and Nielsen[1]). This was combined with Loewi's supposition that acetylcholine is the vagus substance; and after it had been demonstrated upon the isolated hearts of frogs and rabbits that following the administration of strophanthin the same dose of acetylcholine produced a more pronounced bradycardia than before strophanthin was given, the supposition that the digitalis bradycardia is due to a sensitization of the heart muscle to acetylcholine was considered justifiable (Abdon and Nielsen[2]).

Soon afterward, Gremels[3] (1937), experimenting with isolated frogs' hearts, found an augmentation of the chronotropic effect of acetylcholine following the administration of strophanthin, and he showed further that strophanthin increases the effect of acetylcholine on the oxygen consumption and mechanical efficiency of the heart-lung preparation.

It therefore seemed natural to inquire whether any of the other effects of the digitalis substances are due to a sensitization of the heart muscle to acetylcholine.

The digitalis substances cause characteristic changes in the electrocardiogram. If the administration of acetylcholine, as well as vagal stimulation, causes similar changes, those which occur after the administration of digitalis are to be explained by a sensitization of the heart muscle to the acetylcholine liberated by the normal vagal tone.

*From the Medical Clinic B, University of Copenhagen (Chief Physician; Professor E. Warburg, M.D.).

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A direct comparison of the changes in the electrocardiogram brought about in these different ways does not seem to have been made previously, but separate investigations, both on animals and man, have been reported.

Experiments on Man.—The changes in the electrocardiogram of normal adults following the administration of digitalis have been described by Larsen, Neukirch and Nielsen[4] (1937), who concluded from previous investigations and their own results that the most important changes are relative shortening of the electrical systole, depression of the S-T interval, and flattening of the T-waves; bradycardia occurred in only a little more than half the cases. Moreover, it may be added that in one-third of the healthy persons whom they examined, Routier and Puddu[5] (1935) found lower P-waves in Leads II and III after the administration of digitalis. In all of these experiments digitalis itself was used. Regarding strophanthin, Cohn and Levy[6] (1920) state that the effect on the T-waves is only slight or does not appear at all. Kahlson[7] (1928) found that the T-waves were flattened after the intravenous injection of strophanthin, whilst Aschenbrenner[8] (1936) maintained that strophanthin does not cause any changes in the T-waves.

The effect of acetylcholine has been studied by Carmichael and Fraser[9] (1933), who state that in four adults the intravenous injection of this drug caused a slowing of the heart rate, but did not otherwise influence the electrocardiogram.

Vagal stimulation in man is obtained reflexly by pressure on the carotid sinus. Weiss and Baker[10] (1933) found that this procedure caused bradycardia and sometimes complete standstill of the heart; in some cases the electrocardiogram showed auriculoventricular block, and in a few instances ventricular extrasystoles. Nathanson[11] (1933) obtained similar results.

Animal Experiments.—Inasmuch as the effect of the administration of strophanthin and acetylcholine, as well as that of vagal stimulation, has been studied only in dogs, the discussion will be limited to this animal.

According to Selenin[12] (1912), the administration of digitoxin causes bradycardia, auriculoventricular block, and an increase in the size of the T-waves, whilst Bickel and Pawlow[13] (1913) found that the T-waves became lower after the administration of strophanthin, and that bradycardia occurred in only one of four dogs. Cohn and Stewart[14] (1928) administered tincture of digitalis and digifolin and obtained changes in the T-waves and commonly bradycardia. Lastly, Brams[15] (1929) found that different preparations of digitalis caused bradycardia and sometimes delayed auriculoventricular conduction, but that the changes in the T-waves were inconstant.

Goldenberg and Rothberger[16] (1934) have examined the effect of acetylcholine on the electrocardiograms of dogs. They state that the first changes are found in the P-waves; later, auriculoventricular block and sometimes depression of the S-T interval appear, but bradycardia

is seldom seen. The tables of the paper, however, show that in several experiments there was a decided early decrease in cardiac rate.

Vagal stimulation has most often been electrical. There is some disagreement about the results (Einthoven,[17] 1908; Hering,[18] 1909; Rothberger and Winterberg,[19] 1910; Goldenberg and Rothberger,[16] 1934). The disagreement is probably due to the fact that this method of stimulation also involves nerves belonging to the accelerans. Here we can consider, therefore, only the experiments in which the stimulation has been reflex, caused by changing the pressure in the carotid sinus. Kisch and Sakai[20] (1923) produced tachycardia by compressing the carotids of dogs. At the moment pressure was released, and the pressure inside the carotid sinus increased, the cardiac rate again became slow. The paper gives an illustration of an electrocardiogram taken during such an experiment which shows that the P-waves grew lower during the period of bradycardia.

If the experimental results cited above be compared, it may be seen that there is a certain resemblance among the electrocardiographic changes obtained in these different ways, but that they are not by any means in complete agreement. This may perhaps be explained by the fact that the three different kinds of experiments were not carried out on the same subject, so that the dissimilarities could be due to individual variations in mode of reaction. Therefore, in our investigation the changes in the electrocardiogram which occurred following the administration of strophanthin and of acetylcholine and during vagal stimulation caused by pressure on the carotid sinus or on the eyeball were compared in successive experiments on the same person.

TECHNIQUE

The persons used for the experiments were male adults who did not present any subjective or objective signs of disease of the circulatory system. There were no auscultatory, roentgenologic, or electrocardiographic abnormalities, and the blood pressure was normal in each instance.

During the examination the subject lay in bed. The experiments with strophanthin were carried out in the morning. A light breakfast was given, after which the subject rested for about an hour in the room in which the experiment was to be done. It was first ascertained that the heart rate was constant.

The electrocardiograms were obtained by means of an amplifier apparatus which allows all three leads to be taken simultaneously, Lead III being about half the size of the other two. Each electrocardiogram was standardized so that the introduction of 1 mv. caused a deflection of 20 to 23 mm. The time marking was 0.2 and 0.05 sec. and the speed of the film 8 to 9 cm. per sec. In Lead II the measurement of the intervals was accurate within ± 0.003 sec. In the experiments in which acetylcholine was injected or pressure exerted on the carotid sinus, the last three complexes before and the first three after the onset of bradycardia were measured, and in the strophanthin experiments the mean of five beats before and five beats after injection was calculated (Table I).

Strophanthin was given intravenously in an aqueous solution of 1:2000 (sol. g-strophantini, *Pharmacopea Danica*, 1933). The injection lasted about one minute.

A 5 per cent solution of acetylcholine chloride (Merck) was prepared before each experiment. It was injected intravenously as quickly as possible; the first dose was

0.2 c.c., and the size of each succeeding dose was increased by 0.1 c.c. until an effect was obtained.

The vagus was stimulated reflexly in four of the subjects by pressure on the carotid sinus, and in the fifth by pressure on the eyeball.

Inasmuch as the effect of strophanthin is protracted, the experiments were carried out in the following order: (1) Pressure on the carotid sinus, (2) injection of acetylcholine, and (3) injection of strophanthin.

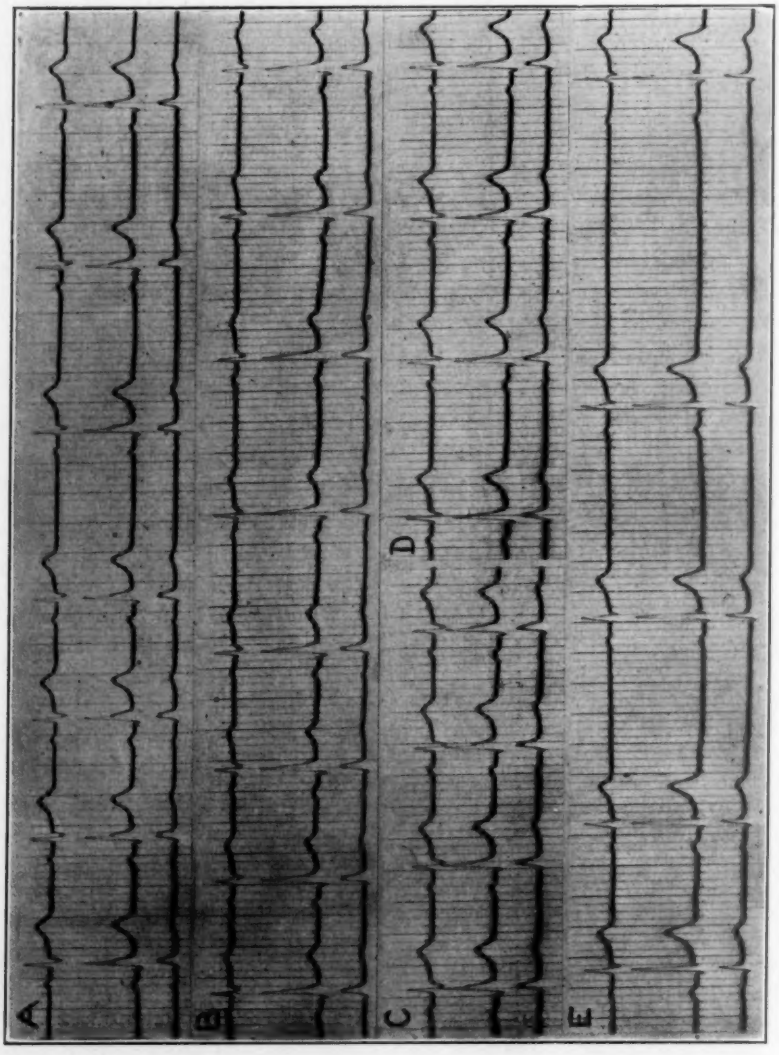

Fig. 1.—Electrocardiograms made during vagal stimulation, during injection of acetylcholine, and before and after injection of strophanthin. *A*, Vagal stimulation (pressure on carotid sinus). *B*, Injection of acetylcholine. *C*, Before injection of strophanthin. *D*, After injection of strophanthin. *A*, *B*, *C* and *D* are from the same person (Subject 1). *E*, vagal stimulation (pressure on eyeball) in another person (Subject 5).

RESULTS

The results are summarized in Table I. This table shows that during pressure on the carotid sinus there was a pronounced bradycardia, and at this time the electrical systole (Q-T interval) was either unchanged or so little prolonged that it was obviously relatively shortened (Fig.

TABLE I

CHANGES IN THE ELECTROCARDIOGRAM DURING PRESSURE ON THE CAROTID SINUS OR THE EYEBALL, FOLLOWING INJECTION OF ACETYLCHOLINE AND OF STROPHANTHIN

SUBJECT	EXPERIMENT	HEART BEAT	R-R_2 IN SEC.	FOLLOWING Q-T_2 IN SEC.	CHANGES IN OTHER PARTS OF ELECTROCARDIOGRAM
1.	Pressure on carotid sinus	3 beats immediately before pressure	0.748 0.808 0.786	0.349 0.357 0.357	
		3 beats during pressure	0.994 0.946 0.976	0.361 0.367 0.373	None
	Pressure on carotid sinus	3 beats immediately before pressure	0.820 0.787 0.793	0.388 0.388 0.391	
		3 beats during pressure	1.110 1.099 1.075	0.391 0.391 0.402	P_2 lower and more pointed, P_3 from positive to negative
	Acetylcholine, 15 mg. intravenously	3 beats immediately before injection	0.911 0.905 0.863	0.393 0.387 0.390	
		3 beats immediately after injection	0.929 1.018 0.946	0.387 0.387 0.393	None
	Acetylcholine, 35 mg. intravenously	3 beats immediately before injection	0.862 0.890 0.862	0.369 0.372 0.372	
		3 beats immediately after injection	1.156 1.207 1.100	0.375 0.378 0.378	P_2 lower and more pointed, P_3 lower
	Strophanthin, 0.25 mg. intravenously	Average of 5 beats before injection	0.796	0.366	
		Average of 5 beats 12 min. after inj.	0.879	0.366	None
	Strophanthin, 0.50 mg. intravenously	Average of 5 beats before injection	0.766	0.380	
		Average of 5 beats 5 min. after inj.	0.968	0.386	P_2 lower and more pointed, P_3 from positive to negative
2.	Pressure on carotid sinus	3 beats immediately before pressure	1.012 1.073 1.067	0.393 0.396 0.387	
		3 beats during pressure	1.311 1.262 1.201	0.387 0.396 0.393	None
	Acetylcholine, 20 mg. intravenously	3 beats immediately before injection	1.009 1.021 1.024	0.388 0.385 0.394	
		3 beats immediately after injection	1.810 2.795 1.290	0.398 0.391 0.406	P_2 higher, P_3 from diphasic to positive
	Strophanthin, 0.50 mg. intravenously	Average of 5 beats before injection	0.816	0.350	
		Average of 5 beats 12 min. after inj.	0.879	0.347	None

TABLE I—CONT'D

SUBJECT	← EXPERIMENT	HEART BEAT	R-R_2 IN SEC.	FOLLOWING Q-T_2 IN SEC.	CHANGES IN OTHER PARTS OF ELECTROCARDIOGRAM
3.	Pressure on carotid sinus	3 beats immediately before pressure	0.799 0.799 0.775	0.364 0.362 0.356	
		3 beats during pressure	1.120 1.096 1.067	0.362 0.356 0.362	P_2 and P_3 more pointed
	Acetylcholine, 35 mg. intravenously	3 beats immediately before injection	0.600 0.603 0.609	0.329 0.326 0.320	
		3 beats immediately after injection	0.845 0.956 0.956	0.333 0.338 0.338	P_2 more pointed, P_3 more pointed and lower
	Strophanthin, 0.25 mg. intravenously	Average of 5 beats before injection	0.740	0.346	
		Average of 5 beats 8 min. after inj.	0.893	0.351	P_3 more pointed
4.	Pressure on carotid sinus	2 beats immediately before pressure	0.694 0.742	0.375 0.380	
		3 beats during pressure	1.002 1.008 0.980	0.380 0.375 0.386	P_2 lower, P_3 from positive to negative
	Acetylcholine, 30 mg. intravenously	3 beats immediately before injection	0.838 0.838 0.838	0.371 0.374 0.374	
		3 beats immediately after injection	0.906 0.974 0.971	? 0.375 0.372	None
	Strophanthin, 0.40 mg. intravenously	Average of 5 beats before injection	0.814	0.387	
		Average of 5 beats 15 min. after inj.	1.033	0.396	P_3 narrower
5.	Pressure on eyeball	3 beats immediately before pressure	0.962 0.962	0.364 $P\text{-}Q_2 = 0.167$ 0.370 $P\text{-}Q_2 = 0.167$ 0.370 $P\text{-}Q_2 = 0.170$	
		3 beats during pressure	1.349 1.393 2.182	0.375 $P\text{-}Q_2 = 0.167$ 0.372 $P\text{-}Q_2 = 0.191$ 0.380 $P\text{-}Q_2 = 0.287$	P_2 and P_3 lower and lower
	Acetylcholine, 32.5 mg. intravenously	3 beats immediately before injection	0.829 0.781 0.784	0.351 0.347 0.347	
		3 beats immediately after injection	0.927 0.994 0.963	0.347 0.351 0.351	None
	Strophanthin, 0.25 mg. intravenously	Average of 5 beats before injection	0.870	0.354	
		Average of 5 beats 12 min. after inj.	1.004	0.363	None

1*A*). When bradycardia was pronounced the P-waves were flattened in Leads II and III, but no changes occurred when the bradycardia was less pronounced. In one experiment on Subject 1 there was moderate bradycardia without changes in the P-waves, but when, in another experiment, the bradycardia was more pronounced, the P-waves were flattened in Leads II and III (Table I). Subject 5 responded to pressure on the eyeball with a great decrease in cardiac rate, accompanied by flattening of the P-waves in Leads II and III, and the slower the rate, the greater the flattening. Simultaneously, the auriculoventricular conduction was delayed in proportion to the decrease in cardiac rate (Fig. 1*E*). The other waves and intervals of the electrocardiogram did not change.

The intravenous injection of acetylcholine was followed by the same changes, except that auriculoventricular conduction was never delayed (Fig. 1*B*). As in the experiment with carotid sinus stimulation, the changes in the P-waves did not appear until the bradycardia became pronounced (Table I, Subject 1). In one subject (No. 2) the P-waves became higher, but in all of the others they grew smaller.

The injection of strophanthin was followed, after a very short interval, in some cases less than one minute, by a definite decrease in cardiac rate which became more pronounced during the succeeding minutes; the Q-T interval either remained unchanged or was inconsiderably prolonged, i.e., there was a relative shortening of electrical systole (Fig. 1*C* and *D*). The changes in the P-waves were the same as those which occurred after carotid pressure and the injection of acetylcholine (flattening in Leads II and III when the bradycardia was pronounced, no change when the rate was only slightly decreased [Table I, Subject 1]). In none of the cases were other changes found, especially the T-waves were not altered, neither was auriculoventricular conduction delayed, within twenty-four hours after the injection.

DISCUSSION

The changes in the electrocardiogram during pressure on the carotid sinus and the eyeball (bradycardia, relative shortening of the Q-T interval, flattening of the P-waves in Leads II and III in cases of pronounced bradycardia, and a single instance of delayed auriculoventricular conduction) were essentially the same as those observed by previous investigators. It is true that relative shortening of the electrical systole has not been mentioned previously, but it is to be seen in the electrocardiograms which have been published. The extrasystoles which others have observed did not occur in our experiments, possibly because of individually different modes of response.

The changes following intravenous administration of acetylcholine corresponded to those produced by pressure on the carotid sinus and eyeball, except that delayed auriculoventricular conduction was not observed. This was probably because of the small amounts of acetylcholine used, for it has been shown in animal experiments that it may have this effect.

The changes following the intravenous administration of strophanthin corresponded to those produced by acetylcholine, viz., bradycardia, relative shortening of electrical systole, and, when the bradycardia was pronounced, flattening of the P-waves in Leads II and III. These results agree with those obtained by investigators who have used digitalis, except that with digitalis there were also changes in the T-waves, and sometimes delayed auriculoventricular conduction and extrasystoles. It has previously been demonstrated that the T-waves are not affected by the administration of strophanthin. The fact that the other changes were not observed in the present experiments may be explained by the well-known individual variations in response to digitalis substances, or by assuming that the doses of strophanthin which were used were too small to effect them.

It is seen that in the same subject the electrocardiographic responses to strophanthin, acetylcholine, and vagal stimulation were identical.

Goldenberg and Rothberger[16] have compared the electrocardiographic changes following the administration of acetylcholine and vagal stimulation in dogs, cats, and rabbits, and have not found complete agreement, but nevertheless they draw the conclusion "dass der Vagusstoff mit dem Acetylcholin identisch ist oder ihm wenigstens sehr nahe steht." As they themselves point out, the difference is most likely due to the fact that electrical stimulation of the vagus also stimulates the nerves belonging to the accelerans. In the experiments presented here, the electrocardiographic changes following acetylcholine and reflex augmentation of the vagal tone have been compared and found to be identical, which speaks in favor of the supposition that acetylcholine is the vagus substance.

It was mentioned in the introduction that the bradycardia following the administration of digitalis is supposed to be caused by a sensitization of the heart muscle to acetylcholine. Further, it was stated that strophanthin increases the effect of acetylcholine on the oxygen consumption and mechanical efficiency of the heart-lung preparation. It was therefore considered natural to inquire whether other effects of digitalis might be explained by acetylcholine sensitization. The present investigation demonstrates that the changes occurring in the electrocardiogram following the injection of acetylcholine and strophanthin in successive experiments on the same person are identical. It therefore seems justifiable to assume that the changes in the electrocardiogram following the administration of strophanthin are caused by sensitization of the heart muscle to the acetylcholine liberated by the normal vagal tone.

SUMMARY

1. In normal adults the administration of strophanthin, of acetylcholine, and vagal stimulation cause the same electrocardiographic changes in the same subject, viz., bradycardia, relative shortening of electrical systole, and, when the bradycardia is pronounced, changes in the P-waves in Leads II and III.

2. The fact that the changes in the electrocardiograms following vagal stimulation and the administration of acetylcholine are identical indicates that acetylcholine is the vagus substance.

3. The changes in the electrocardiogram following the administration of strophanthin may be harmonized with the hypothesis that strophanthin sensitizes the heart muscle to acetylcholine.

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VARIATIONS IN A-V AND V-A CONDUCTION DEPENDENT UPON THE TIME RELATIONS OF AURICULAR AND VENTRICULAR SYSTOLE: THE SUPERNORMAL PHASE

EDWARD M. KLINE, M.D., JEROME W. CONN, M.D., AND FRANCIS F. ROSENBAUM, M.D.
ANN ARBOR, MICH.

IN 1912, Adrian and Lucas[1] designated as the "supernormal phase" a biological phenomenon which they demonstrated in injured excitable tissue. They found that there was a short period during recovery from a previous stimulus in which the tissue became hypersensitive to new stimuli. They showed, further, that this supernormal excitability of nervous tissue was accompanied by a supernormal variation in conductivity. For example, it was shown that an impulse which was ordinarily unable to traverse a depressed zone in a nerve was conducted if it followed a transmitted impulse by an interval of 0.015 to 0.1 second. Adrian[2] pointed out later that an acid medium was necessary for the existence of the supernormal phase.

Ashman[3] produced varying degrees of A-V block in the turtle heart and observed the existence of a supernormal phase in some of the specimens that had been handled repeatedly. He produced an A-V block which was just complete for impulses arriving every fifteen to twenty seconds. When, however, an auricular impulse was sent in about three or four seconds after one of the regularly blocked impulses, it was transmitted. In other words, when an impulse was timed to fall in the supernormal phase of the preceding blocked impulse, it traversed a block through which it could not pass at any other time. Ashman showed, too, that if one impulse passed the block, the following impulses could also be transmitted providing that each impulse occurred during the supernormal phase of the preceding beat.

The existence of a supernormal phase in the human heart was first suggested by Lewis and Master.[4] In their first case, one of complete heart block, A-V transmission occurred whenever the P-wave fell between the summit and the end of the T-wave of the preceding idioventricular systole. This zone, which they likened to the supernormal phase of Adrian and Lucas, was found to lie between the limits of 0.425 and 0.708 second after the initial movement of the QRS complex. In their second case, one of partial heart block with dropped beats, the zone of effective auricular impulses could not be so sharply defined.

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor. This study was assisted by a grant to Frank N. Wilson from the Horace H. Rackham School of Graduate Studies.
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Wilson and Herrmann[5] reported a case of paroxysmal complete heart block which is strikingly similar to the first case described in this article. The data pertaining to this case were re-examined and again reported by Ashman and Herrmann,[6] who found that periods of complete heart block were preceded by periods of gradual auricular slowing. When the length of the cardiac cycle measured from 0.90 to 1.10 seconds, a period of complete heart block followed. Such periods of block were usually interrupted when an auricular systole followed an idioventricular beat by 0.31 to 0.795 second. A critical zone during which the conducting mechanism was reactive to an auricular impulse was therefore present.

Wolferth[7] reported a case of complete heart block with occasional ventricular responses. He found that when auricular systole occurred 0.45 to 0.74 second after the beginning of the preceding QRS complex, the impulse was transmitted. Wolferth stated that although a supernormal recovery phase could explain the occasional transmitted beat, he preferred to attribute it to an improved nutritional state of the depressed zone during that short period of the cardiac cycle. His chief reason for rejecting the concept of the supernormal phase was the fact that at the time of his report no good evidence existed that a supernormal phase occurred in the mammalian heart.

The purpose of this report is to demonstrate in two cases of heart block the existence of a supernormal phase in conductivity. In the first case an impulse arising in the ventricle frequently established in the depressed zone a supernormal phase during which an auricular impulse passed. This successful A-V conduction produced another supernormal phase during which the next auricular impulse was transmitted. In the second case, impulses arising in the auricle produced in the depressed zone a supernormal phase permitting retrograde conduction.

CASE 1.—E. P., a 45-year-old, white male laborer, was admitted to the University Hospital Sept. 21, 1937, complaining of fainting spells. He stated that he had enjoyed good health until six months before admission, when he experienced his first attack of syncope. Attacks had become more frequent so that they occurred almost daily. During attacks he had noticed some irregularity of the heart which he described as "missed beats." There was no history of rheumatic fever or syphilis.

On physical examination, the patient was a well-developed adult male who did not appear severely ill. On several occasions during the examination there occurred transient pronounced pallor of the face, accompanied by a staring facial expression and momentary disorientation. During these attacks, which lasted only a few seconds, the patient was pulseless. In similar but more severe attacks, syncope occurred and ventricular asystole lasted as long as five seconds. Recovery was characterized by intense flushing of the face and the return of normal cardiac rhythm. Except for the cardiovascular findings to be described, the physical examination revealed no abnormalities. The pulse was small and sustained. The blood pressure in the left arm was 138/110, and in the right arm 108/92. The heart was not enlarged on percussion. A loud, rough systolic murmur, transmitted to the vessels of the neck, was heard at the aortic area, where a systolic thrill could be felt. Along the left border of the sternum in the third intercostal space a soft, blowing, high-pitched, diastolic murmur was heard. Both aortic stenosis and aortic insufficiency

were thought to be present. At times, when the beating was irregular, auricular sounds could be heard to the left of the sternum (Fig. 4*A*). There were no signs suggesting congestive cardiac failure.

The urine, blood, and stool were normal. The blood Kahn reaction for syphilis was negative. An orthodiagram revealed definite cardiac enlargement; the frontal plane area was 38 per cent and the total transverse diameter 25 per cent above the average for normal subjects of the patient's height and weight. No calcification of the aortic valve could be made out. Roentgenologic examinations of the spine, soft tissues of the neck, and upper gastrointestinal tract demonstrated no abnormalities.

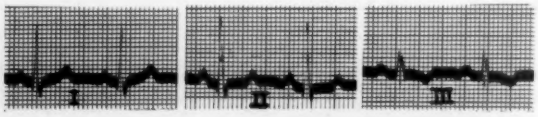

Fig. 1.—Case 1. Sept. 21, 1937. Day of admission. No spontaneous attacks. Carotid sinus pressure not applied.

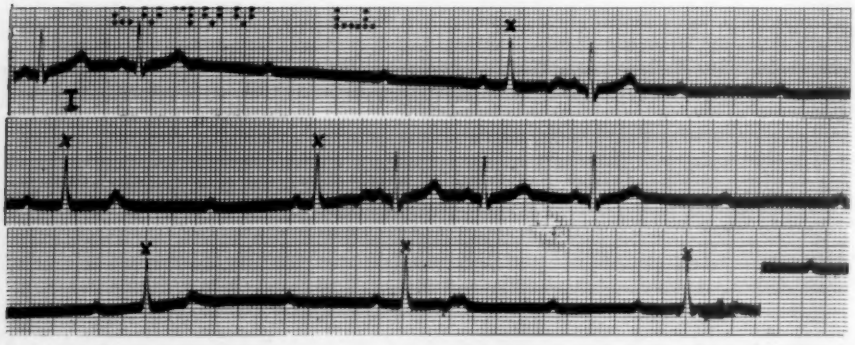

Fig. 2.—Case 1. Sept. 22, 1937. Lead I taken during spontaneous attacks of syncope. Idioventricular beats marked X. Continuous tracing.

The first electrocardiogram, taken when the patient was having no spontaneous attacks, was normal (Fig. 1). The heart rate was 83 per minute and the P-R interval 0.18 second. On the following day there were frequent spontaneous Adams-Stokes attacks. These were relieved by the hypodermic injection of 0.5 c.c. of adrenalin hydrochloride (1:1000 dilution). The electrocardiogram (Fig. 2) taken during these seizures showed repeated intervals of complete heart block associated with ventricular standstill or very slow idioventricular rhythm. The periods of complete heart block were separated by short intervals of normal rhythm. Similar episodes of complete heart block could be induced by carotid sinus pressure. Electrocardiograms were taken to demonstrate the effect of carotid sinus stimulation before (Fig. 3*A*) and after (Fig 3*B*) the injection of 0.5 c.c. of adrenalin hydrochloride. These indicate that the drug prevented prolonged ventricular standstill by inducing the prompt onset of idioventricular beats.*

Figure 4*A* is a record taken 30 minutes after the hypodermic injection of 0.0012 gm. of atropine sulfate. There is no essential difference between this curve and those showing intermittent heart block. Twenty minutes after a second, similar

*From the examination of Fig. 3*B* it may not be at once apparent that complete A-V dissociation is present. The presence of idioventricular beats is indicated by variations in the form of the QRS deflections. These beats are represented by the ventricular complexes which show the larger R-waves and smaller S-waves.

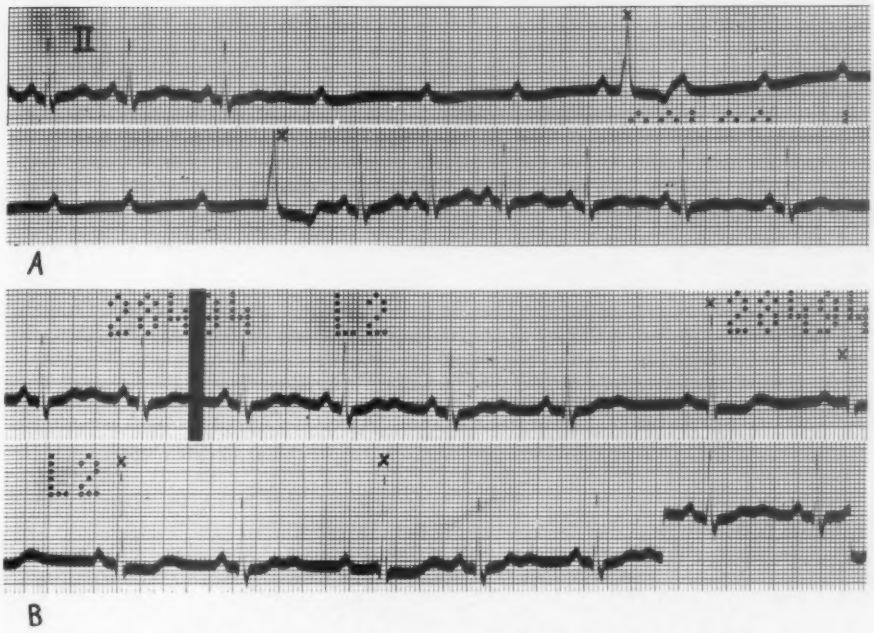

Fig. 3.—Case 1. Sept. 23, 1937. Lead II. *A*, before adrenalin; *B*, after adrenalin. Note the long ventricular asystole after carotid stimulation, in *A*. The heavy vertical line in *B* represents left carotid pressure. Idioventricular beats marked X. A_1 and A_2 continuous. B_1 and B_2 continuous.

dose of atropine sulfate, however, the ventricles (Fig. 4*B*) responded normally to the auricular impulses. At this time the normal rhythm could not be disturbed by carotid sinus stimulation (Fig. 4*C*).

Ephedrine sulfate in doses of 0.025 gm. four to six times daily for a period of six days failed to cause any change in the cardiac mechanism or in the frequency

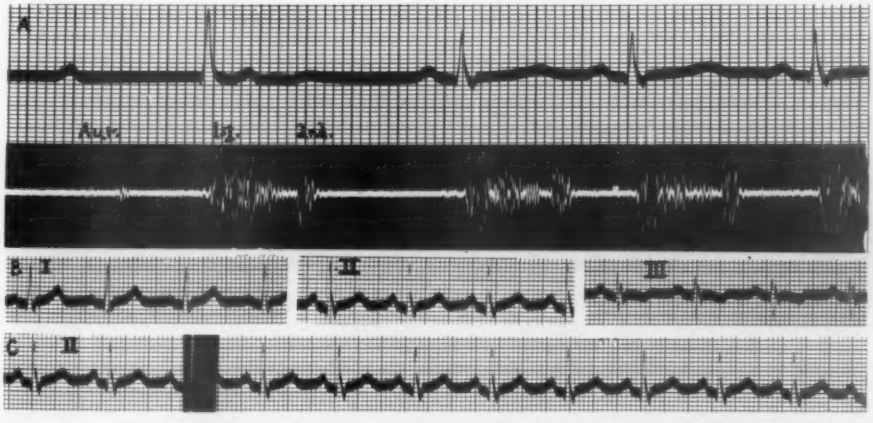

Fig. 4.—Case 1. Sept. 24, 1937. *A*, thirty minutes after atropine sulfate subcutaneously. Note the double auricular sound and the coarse murmur throughout systole. Microphone placed in the third intercostal space, left of sternum. Idioventricular beat in *A*. *B*, twenty minutes after second dose of atropine sulfate. Normal rhythm undisturbed by carotid sinus stimulation in *C*. Heavy vertical line in *C* represents left carotid pressure.

of the periods of asystole. Atropine sulfate by mouth in doses of 0.0004 gm. three to four times daily for a period of five days was also without demonstrable effect.

On Oct. 13, 1937, twenty-three days after the patient entered the hospital, the electrocardiogram showed for the first time partial heart block with three to one response and ventricular escape after each dropped beat (Fig. 5). Except for a brief period of one to one response which resulted from carotid sinus stimulation on Oct. 25, 1937, partial heart block persisted throughout the remainder of the period of hospitalization. With this change in the cardiac mechanism the syncopal attacks disappeared despite increased exercise and frequent carotid sinus stimulation. The patient was discharged from the hospital Oct. 27, 1937. At a check-up examination on April 4, 1938, he stated that he had been working and had had no attacks since leaving the hospital. At this time the electrocardiogram showed complete heart block with abnormal ventricular complexes.

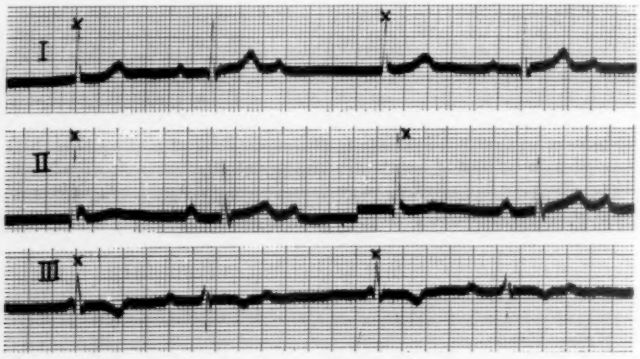

Fig. 5.—Case 1. Oct. 13, 1937. Partial heart block with ventricular escape. Similar to all records obtained during the remainder of hospital course. Idioventricular beats marked X.

Examination of those electrocardiograms showing complete heart block demonstrates several constant relationships. First, complete heart block interrupted the normal rhythm only when there was auricular slowing (Figs. 2, 3*A*, 3*B*), regardless of whether this occurred spontaneously or as the result of carotid sinus stimulation. Secondly, normal rhythm was never re-established unless the first transmitted auricular impulse was preceded by an idioventricular beat (Figs. 2, 3, 4). Since not all idioventricular beats were followed by a resumption of one to one response, we compared the time relations of those beats which were followed by resumption of normal rhythm with those which were not.

In order to study these phenomena, two types of measurements were made. All P-P intervals were measured and placed in two groups. In one group were those which were followed by a conducted auricular impulse and in the second were those which were not. Measurements from the initial deflection of the QRS complex of each idioventricular beat to the following P-wave were treated in a similar manner.

From the first set of figures a chart (Chart I) was constructed after the method of Lewis and Master.[4] This chart shows clearly that the transmitted auricular impulses fall within a definite zone. The upper

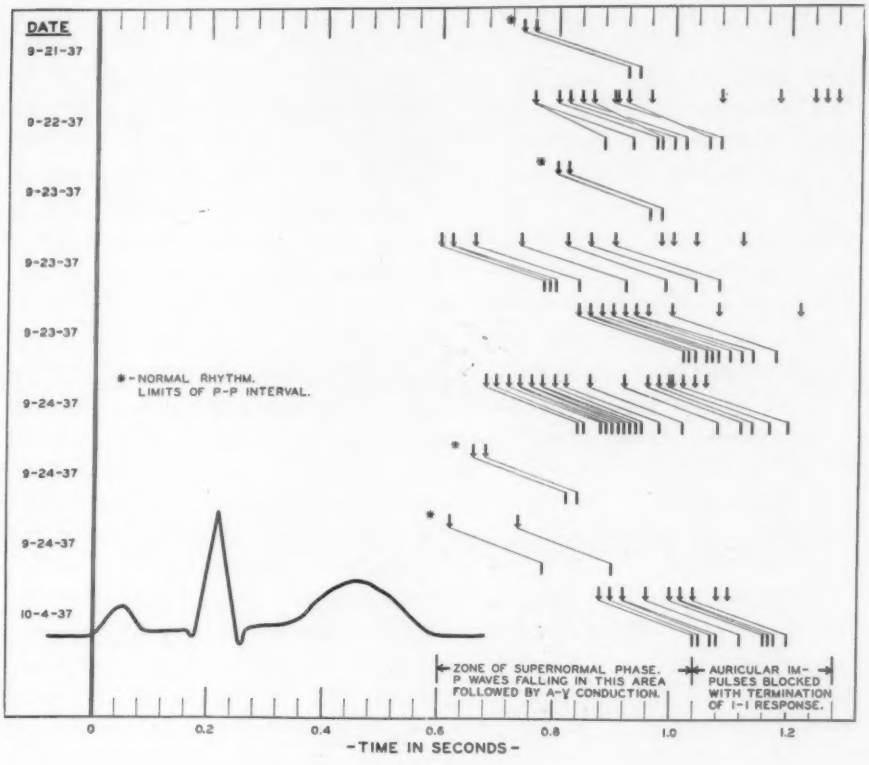

Chart I.

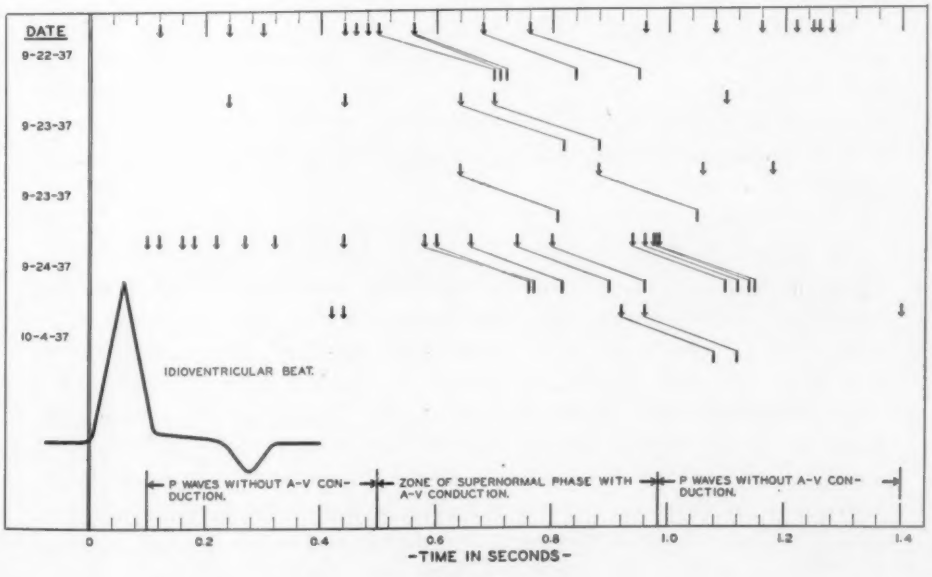

Chart II.

limit of this zone lies between 0.92 second and 1.04 seconds, the lower limit lies at least 0.6 second after the preceding P-wave. No opportunity was afforded to test the lower limit further. Although all of the P-R intervals are within normal limits (varying from 0.12 to 0.19 second) there is no apparent correlation between the length of the P-R interval and the position any particular transmitted impulse occupies within the zone specified. This is in contrast to the findings of Lewis and Master,[4] who reported in their first case a gradual lengthening of the P-R interval from 0.120 to 0.168 second as the upper limit of the "responsive phase" was reached.

In a similar way it may be demonstrated (Chart II) that there is resumption of one to one response when the P-wave follows an idioventricular beat by an interval of at least 0.50 second. When this interval is 0.90 second transmission frequently fails, and when it is 0.98 second it invariably fails. In as much as failure of A-V conduction is always associated with auricular slowing and is never re-established unless an idioventricular beat occurs, it is clear that fatigue and recovery of the junctional tissues do not explain the observed phenomena.

Although there was apparently a pronounced vagal instability, the variations in vagal tone which occurred are not sufficient to explain the observations made. An increase in vagal tone might explain the onset of the block, but a decrease in vagal tone cannot explain the return of normal conduction. In all instances ventricular standstill was accompanied by auricular acceleration; yet in no instance (this is tested twenty-one times) was there re-establishment of A-V conduction until an idioventricular beat occurred.

We believe, therefore, that a supernormal phase was present during the recovery period of the junctional tissues. The characteristics of the tissue in the region where block occurred were such that the penetration of an impulse into this region from below, or the successful transmission of an impulse from above, was the only circumstance which induced supernormal conductivity. As might be anticipated, the boundaries of the interval during which the depressed region conducted varied slightly from day to day, particularly its upper boundary. Nevertheless, the limits of this interval remained remarkably constant, considering the variety of circumstances under which observations were made.

Chronic complete heart block ultimately occurred, and it is probable that the conduction defect was due to an organic lesion. Since it has been adequately shown that the existence of a supernormal recovery phase is an abnormal phenomenon associated with tissue injury, it is logical to assume that conditions were such as to favor its production in this case. In none of our records in which there was partial block was there evidence that a supernormal phase played a role in determining the cardiac mechanism. Rather, there were indications that recovery and fatigue were acting in the ordinary way; in one instance, when

auricular slowing was produced by carotid sinus pressure, there was continuous, although prolonged, A-V conduction for a short period (Fig. 6).

A review of the electrocardiograms published by Cheer and T'Ang,[8] and Sachs and Traynor,[9] which show paroxysmal complete heart block, suggests that the peculiarities of conduction which they observed might also be explained by assuming the occurrence of a supernormal phase during the recovery period of the junctional tissues.

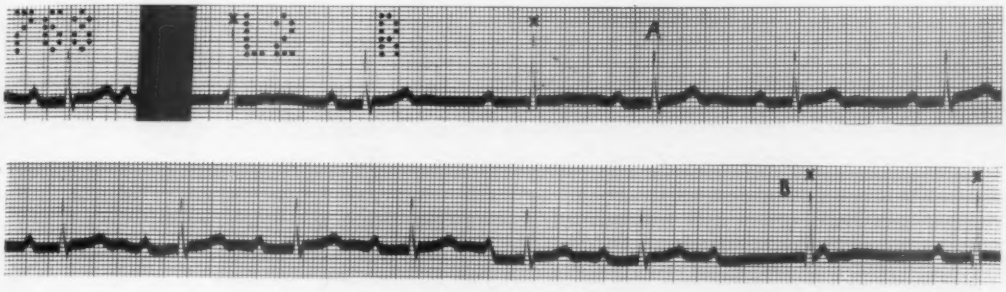

Fig. 6.—Case 1. Oct. 25, 1937. Beginning at *A* and terminating at *B* are eighteen responses of the ventricle to the slowed auricle. Result of right carotid pressure. Heavy vertical line represents right carotid pressure. Idioventricular beats marked X. Record is not continuous.

Case 2.—O. S., a 68-year-old white woman, was admitted to the University Hospital for the first time on Sept. 8, 1933. She then complained of intermittent vaginal bleeding which had been present for two years. There were no symptoms referable to the cardiovascular system.

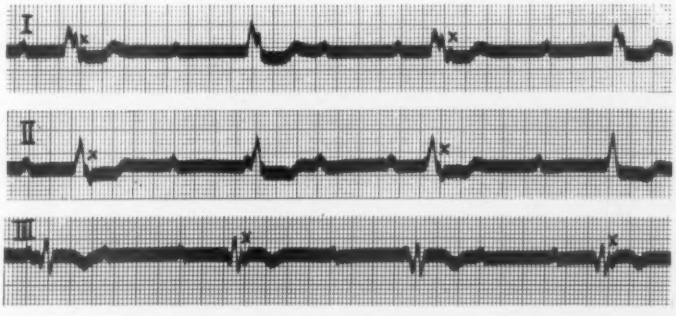

Fig. 7.—Case 2. Dec. 8, 1933. Complete heart block with abnormal ventricular complexes. Ventricular rate 35 per minute. QRS interval 0.14 second. Premature P-waves marked X in all leads, inverted in II and III. QRS-P interval 0.12 to 0.14 second.

On physical examination the patient was very obese. The heart was not enlarged. The heart rate was approximately 84 per minute and the beating was regular. There were no murmurs. The blood pressure was 200/118. A few râles were heard at the bases of the lungs, but there were no other signs suggestive of cardiac failure. Pelvic examination revealed adenocarcinoma of the cervix, a diagnosis proved by biopsy. Radium and deep roentgenotherapy were employed with good immediate result and there has been no recurrence of the tumor.

After leaving the hospital the patient began to notice edema and severe dyspnea. When re-examined on December 7, 1933, the blood pressure was essentially unchanged, but the heart rate was only 37 per minute. The beating was regular. All of the signs of moderate congestive cardiac failure were present. The presence of complete heart block was confirmed by an electrocardiogram (Fig. 7) taken Dec. 8, 1933. The ventricular complexes of this record are strikingly abnormal, and the QRS interval measures 0.14 second. In addition, some of the ventricular complexes are deformed by premature P deflections which are inverted in Leads II and III.

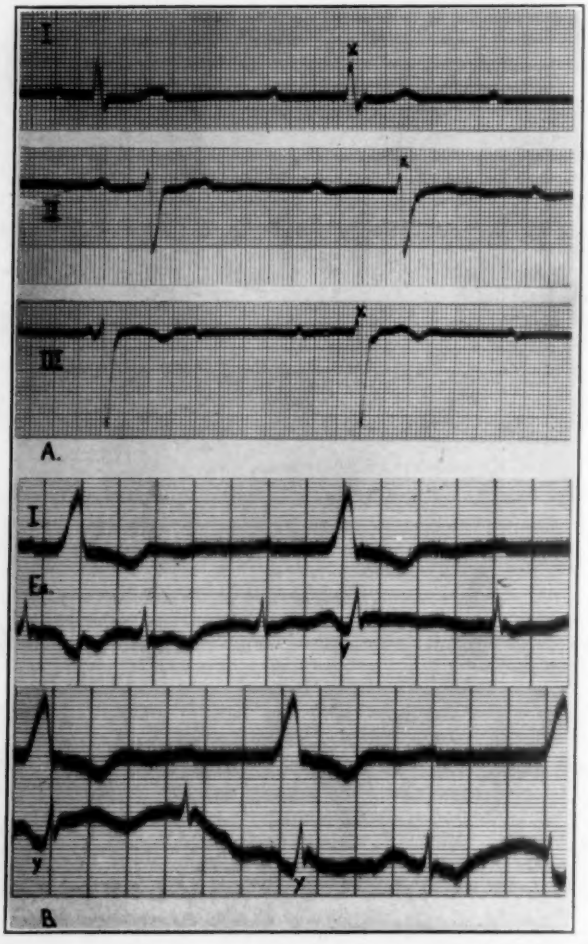

Fig. 8.—Case 2. Dec. 6, 1937. *A*, Complete heart block with abnormal ventricular complexes. Note in all leads slight deformation of the terminal part of the QRS complexes marked X; interpreted as abnormal P-waves. *B*, Esophageal lead. Frequent premature auricular contractions following ventricular beats marked Y. R-P interval measures 0.115 to 0.135 second. Record continuous.

A few days after the patient was admitted to the ward auricular fibrillation developed. The ventricular beating became irregular, indicating that the ventricles were responding to the fibrillating auricles. The ventricular rate was relatively slow and after the longer pauses ventricular escape frequently occurred. The ventricular complexes of the idioventricular beats were of the same form as those recorded previously, but the ventricular complexes of the sequential beats were of a

more normal type. They displayed pronounced left axis deviation, but the QRS interval was about 0.11 second. Deflections of this kind suggest the presence of incomplete left bundle branch block. Digitalis had been given just prior to these developments and when it was discontinued the auricular fibrillation disappeared and normal sinus rhythm returned. There was no further change in the contour of the ventricular complexes.

It was not until four years later that the patient was again examined. At this time complete A-V block was again present. In Lead III (Fig. 8*A*) occasional differences in the termination of the S-wave near the isoelectric line (Fig. 8*A*, marked X) suggest the occurrence of premature inverted P-waves similar in origin to those recorded in the tracings taken four years earlier (Fig. 7). In order to demonstrate auricular deflections to better advantage, esophageal leads were taken. The most satisfactory for our purpose is that taken with the esophageal electrode 35 cm. from the patient's lips (Fig. 8*B*).

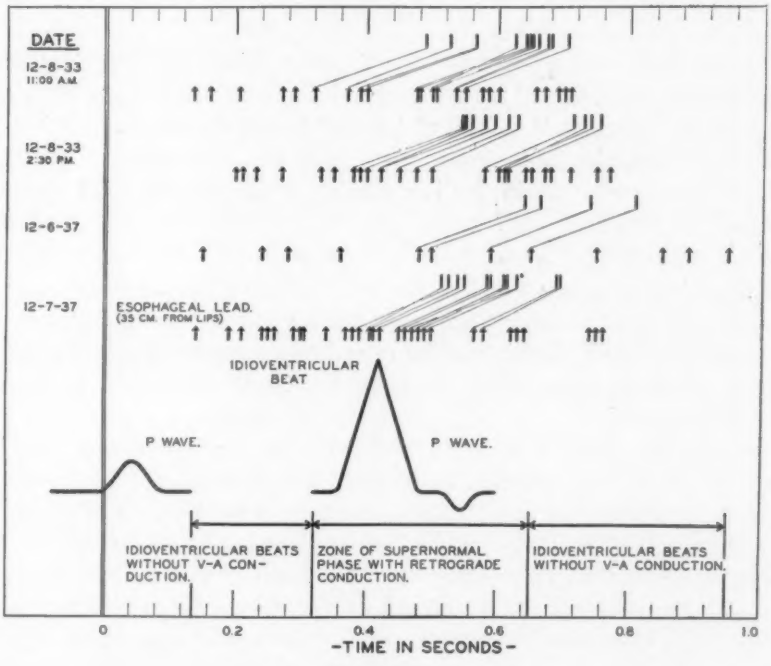

Chart III.

Measurements made from the beginning of each QRS complex deformed by a premature P-wave to the preceding P deflection show that these deformed complexes fall during a well-defined interval. Over the four-year period of observation the limits of this interval are fairly constant. Its extreme limits extend from 0.32 second to 0.65 second after the preceding P-wave.

If we assume that the premature P-waves represent retrograde conduction, an explanation based on the concept of the supernormal phase is suggested. In this instance the supernormal phase is produced by the penetration of the auricular impulse into the region of depressed

conductivity and permits retrograde conduction. A chart (Chart III) illustrating this mechanism has been constructed after the same plan as that used for Case 1.

Cases of a similar kind have frequently been reported in the literature. Some writers (Cohn and Fraser,[10] Wilson and Robinson,[11] and Barker[12]) have considered the abnormal premature P-waves to be the result of impulses arising in the lower auricular or upper junctional tissue. Others (Danielopolu and Danulesco,[13] and Wolferth and McMillan[14]) believed that they were due to the occasional retrograde transmission of one of the idioventricular impulses. In these cases it is possible that supernormal conductivity was present, although the examination of the published tracings does not prove this conclusively.

DISCUSSION

Supernormal conductivity in Case 1 was produced by penetration of a ventricular impulse into the depressed region and by successful A-V transmission through it. It is of interest to point out that during the periods of asystole there was always auricular acceleration until the P-P intervals were within the boundaries of the supernormal phase as outlined in Chart I. However, there was never resumption of A-V transmission until an idioventricular beat occurred. This indicates that auricular impulses were ineffective in modifying the conducting properties of the blocked zone unless they passed completely through it. On the other hand, the idioventricular impulses were able to set up a supernormal phase in spite of the fact that they never passed the region of block.

An opposite situation was present in Case 2. Here auricular impulses which presumably penetrated but did not pass the depressed region were effective in producing supernormal conductivity. In view of what has been said regarding Case 1 it is logical to expect that successful V-A transmission would also produce a supernormal phase. If such were the case, A-V transmission should have been resumed if the following P-wave fell within the supernormal phase produced by the retrograde impulse. Since each retrograde impulse was followed by a compensatory pause before discharge of the next auricular systole, this systole was always too late to reach the depressed region during the supernormal period.

Why a supernormal phase in atrioventricular conductivity should lead in one case to improved A-V conduction and in another case to improved V-A conduction is not altogether clear.

SUMMARY

Two cases of transient complete heart block are reported in which there was a supernormal phase in the conductivity of the depressed region. In the first case, penetration of the depressed zone by an impulse arising in the ventricle produced a supernormal phase during

which A-V conduction occurred. The conducted impulse in turn gave rise to a supernormal phase which permitted the next impulse to pass, so that normal sinus rhythm was established. It was maintained until auricular slowing caused the auricular impulse to fall outside of the period of supernormal conductivity. In the second case, impulses arising in the auricle produced in the depressed zone a supernormal phase which permitted retrograde conduction.

The authors wish to acknowledge their appreciation of the valuable suggestions and assistance of Dr. Frank N. Wilson and Dr. Franklin D. Johnston in this study.

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THE MEASUREMENT IN MAN BY A PNEUMOCARDIOGRAPHIC METHOD OF THE EXCESS OF ARTERIAL OUTFLOW FROM THE CHEST OVER VENOUS INFLOW DURING THE HEART CYCLE

H. A. Blair, Ph.D., and A. M. Wedd, M.D.
Rochester, N. Y.

THE early literature on the pneumocardiogram has been reviewed by Luciani[1] (1911) and by Klewitz[2] (1918). The first description of the negative thoracic pulse is attributed to Buisson, in 1861. Mosso, in 1878, using a Marey tambour connected with the nasal cavities, first satisfactorily recorded intrathoracic pressure changes. In 1887, Luciani observed by means of a balloon in the esophagus those variations in thoracic pressure that are due to the heart's action. These and later observations indicate that during systole more blood leaves the thorax than returns, while later in the cardiac cycle the deficit is made up by an excess of venous return over arterial output. However, contrary views have been expressed which assert that arterial movement is immediately compensated by venous, with the result that the blood content of the thorax is practically constant during the cardiac cycle.

Measurements of intrathoracic pressure changes made to determine the excess of outflow from the chest over inflow are usually calibrated by the method of Wiedemann[3] (1919), in which a manometer connected with the mouth, nose, or trachea records intrathoracic pressure changes. Comparison of the initial excursion with that which results when a known volume is introduced into the recording system by adding a bottle of air forms the basis of calibration. The validity of the method depends on the constancy of the volume of the thoracic cavity, a condition which is probably never fulfilled.

In the method here presented those movements of the chest wall due to the heart beat are recorded with an ordinary pneumograph* connected with a membrane manometer whose movements, when photographed, give records such as Fig. 1*a*, in which an upward deflection corresponds to a diminution of chest volume. Comparison with the electrocardiogram indicates that the thorax collapses for about one-sixth of the cardiac cycle and expands during the remainder. To determine the extent of collapse, the nose is held and a suitable rubber

From the Departments of Physiology and Medicine, School of Medicine and Dentistry, the University of Rochester, Rochester, N. Y.

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*This is a closed rubber tube, 37 cm. long and 2 cm. in diameter, distended by a coil spring, made by the Harvard Apparatus Company. The recording tambour is a segment capsule about 2.5 cm. in diameter, covered with sheet rubber 0.15 mm. thick. The membrane can be kept quite tight and still allow ample excursion of the light beam at 1.5 M.

bulb is connected with the mouth by a glass tube. The bulb is then squeezed to force into the lungs its contained air, or alternatively, it may be allowed to expand from the empty state and thus remove air from the lungs. This procedure brings about a shift in the level of the oscillations due to a change in the volume of the thorax which is equal to the volume of air in the bulb. A comparison of the extent of the oscillations of the record with this shift permits direct measurement of the decrease in volume brought about by the net loss of blood from the thorax during the early part of the cardiac cycle.

There appears to be but one important assumption in this method, namely, that the addition to, or the removal from, the thorax of a given volume of blood will affect the chest wall in the same way as the addition or removal of an equal volume of air. This is equivalent to assuming that the lungs remain in continual apposition to the chest wall and to the thoracic organs and vessels, and that a pressure change occurring in one part of the lungs is readily distributed over the whole. This assumption appears valid. It is, of course, also assumed that the pressure within the lungs returns to its original value after the introduction or removal of the calibrating air. This condition seems to be satisfied except occasionally in subjects who cannot hold their breath without small involuntary respiratory movements. It may be checked, however, by registering the pressure in the mouth when air is introduced or removed, and noting whether that pressure, and therefore the pressure in the lungs, returns to normal, which it will do if the glottis be open. Such a record is shown in Fig. 2 and will be described later.

A typical calibration record, using a bulb of 24 c.c. capacity, is illustrated by Fig. 1*b*. It will be seen that the tracing rises as a result of the removal of air from the thorax by means of the bulb, and that the displayed tracing tends to fall slowly. This is due to a small leak in the system through a short length of thermometer tubing which is introduced so that the light beam will return promptly to the camera when the breath is held. In the original record the base line displacement is 17 mm. and the height of the wave about 25 mm., measured from the point *A* to *B*. Thus the change in the volume of the thorax with the heart beat is $\frac{25}{17} \times 24 = 35$ c.c. Measurement is made from *A* to *B* because the downward wave that just follows the R-wave of the electrocardiogram is due to the apex thrust of the heart. Since this wave varies from a small oscillation in some subjects (e.g. Fig. 1*a*) to a large wave such as that seen in Fig. 1*b* in others, it is clear that it should not be included in the volume change attributed to the movement of blood.

As already mentioned, when the pressure in the lungs is recorded simultaneously and is seen to return to its initial level the method is more reliable. Fig. 2 represents such a record; the upper tracing is

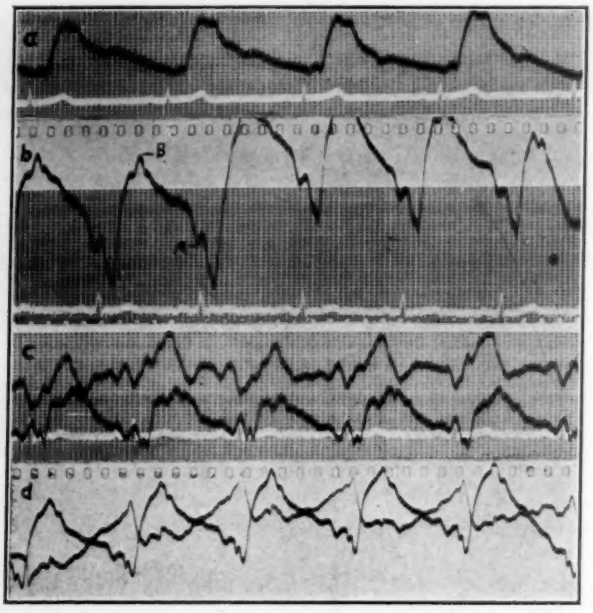

Fig. 1.—*a*, Lead I of the electrocardiogram and a normal pneumocardiogram with the pneumograph just below the sternum. An upward movement is due to collapse of the thorax. *b*, Calibration in another subject. The displacement of the tracing is due to the removal of 24 c.c. of air from the lungs. There is a large apex thrust, shown by the downward movement (expansion of the thorax) occurring just after the R-wave. *c*, Upper record from the mouth with the glottis open, a rise in the tracing denoting a fall in the pressure in the mouth. Lower record, simultaneous pneumocardiogram. *d*, Simultaneous records of the pneumograph on the chest and of the pressure in the mouth with the glottis closed. The tracing from the chest goes lower and that from the mouth gives the left hand peaks of the pairs at the top. All records taken with the subject sitting.

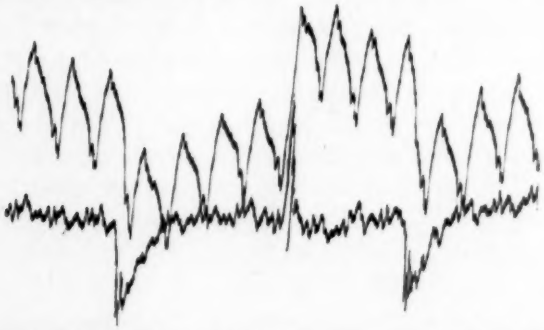

Fig. 2.—Upper tracing, displacement of the pneumocardiogram resulting from the introduction into, or removal from, the thorax of 24 c.c. of air. Lower tracing, the pressure in the mouth and lungs. The large deflections downward in the tracing from the mouth are due to the introduction of 24 c.c. of air into the mouth-lung system. The upward deflection is caused by the removal of 24 c.c. of air. There was a leak in the pneumograph recorder, none in the mouth-pressure recorder.

the pneumogram and the lower is from a manometer connected with the mouth. The first large downward deflection of the tracing from the mouth is due to the introduction of 24 c.c. of air from the bulb; the second large deflection, which is upward, is due to the more rapid removal of 24 c.c., and the third deflection, again downward, to reintro-

ducing 24 c.c. The chest expands or contracts in response to the bulb. There is some drift of the chest tracing because of the leak. It can be seen that the mouth pressure returns to about its initial level in each instance, indicating that the lung pressure does also, since the glottis is open. The evidence for an open glottis is the small oscillation of the mouth tracing, a point which will be discussed later.

By this method of calibration we have measured the excess of arterial outflow over venous inflow during the cardiac cycle in four subjects. For the first, the average of twelve measurements was 26 c.c., the upper and lower limits being 30 c.c. and 23 c.c., respectively. For another subject, four determinations, made on different days, ranged from 26 c.c. to 37 c.c., with an average of 32 c.c. A third subject, on one occasion, gave three values from 25 to 28 c.c., and a fourth, 26 c.c. and 28 c.c. for two estimations. The average value for the four subjects was 28 c.c. Variations are due in part to real variation in output, and in part to inaccuracies in the method. When mouth pressure is recorded simultaneously, the variations are referable largely to the choice of points from which the deflections are measured, and to the effect of the leak, neither of which is likely to amount to more than a few cubic centimeters. In any case, it may be concluded that the excess of output over inflow is of the order of 30 c.c.

These values are much higher than those obtained by the method of Wiedemann.[3] For example, Hamilton[4] (1930) concluded that in man there cannot be more than about 1 c.c. excess of arterial outflow over venous inflow, and that this occurs only during the first sixth of the cardiac cycle. His conclusion necessitates the further one that venous return occurs for the most part only during systole. Likewise, Klewitz and Baumm[5] (1921) reach a similar conclusion from dog experiments; their figures for excess of outflow range from 0.22 c.c. to 0.48 c.c. It is evident that the very factor on which the present method is based, the movement of the thoracic wall in response to internal pressure changes, is just the one which introduces a large error into the Wiedemann method, for any compensatory movement of the chest wall or diaphragm will diminish the pressure changes in the mouth.

Inasmuch as most observations on the pneumocardiogram, including those reported recently, have been made with oral recording, it is desirable to compare simultaneous tracings from the mouth and chest. In the example Fig. 1*c*, the upper tracing is from the mouth with the glottis open and the lower is from the chest wall. It will be noted that the tracing from the mouth begins to rise just after the peak of the R-wave, indicating lowering of mouth pressure, and it continues upward as the chest tracing goes downward. This rise is simultaneous with the beginning of the downward movement of the chest record due to the apex beat. The relationship is explained by the fact that the apex beat, which is associated with an outward movement of the chest wall, lowers

the pressure in the lungs, and so the mouth pressure will begin to decline with the apex beat and continue while ejection takes place, whereas in the chest tracing apex beat and ejection give rise to movements which are opposite in direction. It will also be seen that the pressure in the mouth reaches its minimum before the size of the thorax does. This is to be expected, since the mouth pressure will be low only until the chest walls have collapsed sufficiently to restore the lungs to atmospheric pressure. In other words, the tracing from the mouth registers only the lag of the chest wall and the diaphragm in their movements to compensate for pressure changes in the lungs.

Moreover, the influence on the tracing from the mouth of blood going to the tissues of the mouth and throat, as well as that of air pressure changes in the lungs, must be considered. This is illustrated by Fig. 1*d*, which shows simultaneous tracings from the chest and mouth with the glottis closed. Here it is seen that the pressure in the mouth begins to *increase* rather than decrease just before the chest begins to collapse, reaches a maximum, and then declines slowly. Thus, with the glottis open, lowering of the pressure in the mouth secondary to the lowering in the lungs is compensated to some extent by a rise in mouth pressure produced by the pulse in surrounding tissues. The entry of this factor can be seen as a notch on the rise of the tracing made with the glottis open (Fig. 1*c*), but its importance is difficult to estimate because when the glottis is open the volume of air in the recording system is greatly increased by the addition of the lung volume. Some subjects show more sustained lowering of mouth pressure when the glottis is open than in the illustration used, perhaps because of a tendency for the glottis to close when air is taken from the mouth to the lungs.

Attempts to obtain records with both the mouth and the glottis open were made in order to see whether the thoracic movement was appreciably altered when compensation was possible by air movement through the trachea. Without recording, it is difficult to be certain that the glottis is open, but from records taken when the glottis was thought to be open the chest movement was practically unchanged in amplitude, though perhaps slightly in form. It appears easier for internal pressure changes to move the chest wall than to force air through the trachea.

From such considerations it is clear that the tracing from the mouth alone cannot give an accurate measure of the flow of blood to and from the thorax, and that the assumption of negligible compensation by the chest wall and diaphragm is untenable. Indeed, it appears that the flexibility of the thoracic cage and the diaphragm is so great that it introduces into the calibration by the Wiedemann method an error which amounts to approximately 90 per cent. It may be added that the flexibility of the thorax favors arterial rather than venous flow. While normally the aspiratory action is not very important, if the chest were

rigid the outflow from the chest would exert its aspiratory effect almost entirely on the inflow, and then energy would be lost by the arterial system. Reduced flexibility due to rigidity of the lungs must significantly alter cardiodynamics.

SUMMARY

The movements of the chest wall caused by the heart beat were recorded photographically from an ordinary pneumograph during suspended respiration. To calibrate the excess of outflow of blood from the chest over inflow during the early part of the cardiac cycle the oscillations of the record were compared with the displacement obtained by introducing into the thorax, or removing from it, 24 c.c. of air by way of the mouth. It is concluded that the excess of arterial outflow over venous inflow is approximately 30 c.c. Reasons for the low values, about 1 c.c., which have been obtained previously by tracings from the mouth alone are discussed.

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CIRCULATORY EFFECTS OF INTRAVENOUS INJECTION OF FIFTY PER CENT DEXTROSE AND SUCROSE SOLUTIONS IN PATIENTS WITH HEART DISEASE*

LAURENCE B. ELLIS, M.D., AND JAMES M. FAULKNER, M.D.
BOSTON, MASS.

IN THE practice of clinical medicine and surgery the intravenous administration of 50 per cent dextrose solution is a therapeutic measure commonly employed in a variety of conditions and with various ends in view. Its use has been advocated with the object of supplying needed sugar, of raising arterial blood pressure and increasing blood volume, of reducing intracranial tension, and of effecting diuresis. Dextrose is frequently administered to patients with heart disease either with the purpose of benefiting the cardiac condition itself or as therapy for some other condition when the heart disease is incidental.

In spite of the widespread use of this substance and the numerous clinical reports in the literature, there is a paucity of reported experimental studies dealing with its actual effect on the hemodynamics of the circulation in man.

A number of experimental studies on animals have been reported concerning the effect of hypertonic dextrose solution on the minute-volume output of the heart, the blood volume, the arterial blood pressure, and the heart rate. Kisch,[1] using a 4 per cent dextrose solution in physiologic saline, and Mazzola and Torrey,[2] employing a 50 per cent solution, found that in the cat there was an increase in cardiac output persisting from 30 minutes to two hours. Onozaki[3] found that the injection of 25 per cent dextrose solution produced the same effect in the rabbit. Hamm and Pilcher[4] reported that one and two hours after a large injection (100 c.c. per kilogram body weight) of 50 per cent dextrose solution in dogs the cardiac output was usually somewhat reduced. Several studies[5, 6, 7] have been made in animals indicating that the plasma volume is increased immediately following the injection of hypertonic dextrose solution. Most investigators agree that when hypertonic solutions of dextrose are administered experimentally to animals in quantities proportionally greater than were used in the present study there is a moderate increase in blood pressure after an initial drop, the rise persisting for one to two hours. Unless very large amounts of solution are given the heart rate shows no change, or even decreases.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

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In man the reported work on the effect on the circulation of injecting hypertonic dextrose solutions is very meager. Gibson and Evans[8] found that following the intravenous injection of 50 c.c. of 50 per cent dextrose solution into a normal subject there occurred within five minutes an increase in blood volume of about 200 c.c. Massermann[9] noted no change in arterial blood pressure or heart rate during or following the injection of large amounts (up to 200 gm.) of hypertonic dextrose solution, although Yesko, Passalacqua, and Judd[10] found a transitory increase in systolic blood pressure and heart rate and a decrease in diastolic pressure after the injection of about 1000 c.c. of 1 per cent salt solution containing 10 per cent dextrose.

Certain reported studies concerning the hemodynamic effects of the injection of comparatively large amounts (500 to 1500 c.c.) of isotonic or mildly hypertonic (5 per cent dextrose in normal saline) solutions are pertinent to our study. In the papers of Gilligan, Altschule, and Volk[11] and Altschule and Gilligan[12] it was shown that in persons with normal cardiovascular systems there was an increase in plasma and blood volumes immediately following the injection. The magnitude of this increase was dependent on the rate of injection and might persist for two hours. If the rate of injection exceeded 20 c.c. per minute, considerable increases in venous pressure, cardiac output, and velocity of blood flow, and occasionally in pulse rate and pulse pressure, occurred during the injection. The increase in venous pressure never lasted more than ten to twenty-five minutes.

Caughey[13] and Richards, Caughey, et al.,[14] could demonstrate very little change in venous pressure when 1500 to 2500 c.c. of normal saline were infused into normal individuals at a rate of 50 c.c. per minute, but when cardiac patients were studied a progressive rise in venous pressure occurred.

Recently there have appeared reports advocating the intravenous administration of 50 per cent sucrose solution, rather than dextrose, in certain clinical conditions. Keith, Wakefield, and Power[15] demonstrated that large amounts could be given intravenously to man without toxic effect and that it was excreted quantitatively in the urine within twenty-four hours. Because the sucrose molecule, being larger and less diffusible than dextrose, theoretically should remain in the blood longer, and since it was neither broken down, nor utilized, nor stored in the body, it appeared rational to believe that hypertonic sucrose solutions would be more efficient than dextrose in maintaining blood volume and in causing diuresis, and would not produce the secondary rise in spinal fluid pressure which had been observed following the injection of dextrose. The studies of Bullock, Gregersen, and Kinney[16] on dogs, and the work of Massermann[17] concerning the effect of sucrose on reducing spinal fluid pressure in man, and that of Murphy, Hershberg, and Katz[18] on its action in relieving intracranial tension in patients with severe

arterial hypertension, as well as certain reports regarding its diuretic effect,[19, 20] have tended to confirm the theoretical basis for the value of sucrose. No work on the effect of this substance on the hemodynamics of the circulation has been reported other than the observation that massive injections (300 to 500 c.c.) of a 50 per cent solution produce little effect on the blood pressure.[18]

Although it is generally assumed that the use of either 50 per cent dextrose solution in quantities up to 100 c.c. or of larger amounts of isotonic or mildly hypertonic solutions is a relatively safe procedure, serious reactions have been observed. Clark[21] has reported two deaths after the administration of 500 c.c. of a 10 per cent solution of dextrose in normal saline, and one following a like amount of normal saline. The question always arises whether the mode of injection, the substance itself, or some extraneous factor is responsible for such an untoward happening.

The present study was undertaken to ascertain what changes actually take place in the circulation of cardiac patients as well as of individuals with normal cardiovascular systems during and following the intravenous injection of 50 per cent dextrose and sucrose solutions. From such a study information may be gained regarding the therapeutic effectiveness and possible dangers of this procedure.

METHOD

All procedures were carried out with the patient recumbent following a period of rest long enough to stabilize the arterial blood pressure and the heart rate. The sugar solution was warmed and injected into an antecubital vein at a rate of 10 c.c. a minute. A total of 100 c.c. was given in each instance. Ordinary commercial ampules of dextrose solution were employed. The sucrose used was in part a commercial preparation* and in part consisted of several lots made up in the laboratory by dissolving commercial sucrose in freshly distilled water and sterilizing it by passage through a Berkefeld filter.

Once or twice the subject complained of pain at the site of the injection or along the course of the vein. If this occurred the experiment was stopped. Of the subjects receiving dextrose one complained of slight chilliness forty-five minutes following the injection and one had a mild chill after forty-five minutes. There were more reactions following sucrose. On two occasions mild chilliness occurred about an hour after the injection and in five instances chills, varying from mild to severe, took place in from one to two hours. These chills bore no relationship to the lot of sucrose employed and may well have been caused by the procedure for determining venous pressure, in which it was necessary to infuse saline solution very slowly over a period of about forty-five minutes. Otherwise the patients experienced no subjective sensations during or following the injection. No definite beneficial effect on the patient's clinical state as the result of the administration of the sugar was apparent.

Observations were made of the arterial and venous blood pressures, the heart rate, and relative changes in the plasma volume as estimated by alterations in the plasma protein and hematocrit values. The arterial blood pressure was measured with a mercury manometer by the auscultatory method. The venous pressure was obtained

*We are indebted to Eli Lilly and Company for supplying us with ampules of 50 per cent sucrose solution.

by the direct method of Moritz and von Tabora[22]; readings were taken at one- to two-minute intervals throughout the period of injection and usually for about thirty minutes thereafter. For any subsequent determinations the needle was reintroduced. A total of about 50 c.c. of physiologic saline solution was injected while obtaining the venous pressures, an amount insufficient to produce any demonstrable effect on the venous pressure.

Relative changes in plasma volume were estimated by determining the hematocrit and plasma protein values at intervals following the injection of sugar. Since the total protein content of the plasma can be assumed to be unchanged during the period of the experiment, any change in its concentration is a proportional reflection of change in the water content of the plasma resulting from the injection. The plasma proteins were determined by a modification of Howe's method.[23]

Changes in hematocrit values similarly reflect changes in the plasma volume, but, because of the possibility that the hypertonic solution may cause some shrinkage in cell volume or that the procedure might conceivably alter the total number of circulating erythrocytes, this determination is probably a much less accurate estimate of change in plasma volume than is the calculation of change in the plasma proteins. The proportional alteration in plasma volume as estimated by hematocrit change was calculated from a slight modification of the formula of Landis, Jonas, Angevine, and Erb[24]:

$$\text{Percentage change in plasma volume} = \left[100\ \frac{C}{C_1} - 100\right] \times \frac{1}{100\text{-}C}, \text{ where C equals}$$

relative cell volume of blood before the injection of sugar, and C_1 equals relative cell volume following injection.

The estimation of changes in plasma volume by plasma protein determinations has been compared by Gilligan, Altschule, and Volk[11] with the determination of blood volume by the method of Gibson and Evans[8] and found to be accurate. A full discussion of this subject is given in the paper of Gilligan, Altschule, and Volk.[11]

Thirty-six studies were made, nineteen with dextrose and seventeen with sucrose. Two of the subjects to whom dextrose was given had no evidence of cardiovascular disease; the remainder had heart disease. Of these, three were convalescent from congestive failure, and two had suffered coronary thromboses four and six weeks previously but did not have congestive failure. The remainder were suffering from congestive failure varying in degree from mild to very severe. The majority of this group had both right- and left-sided failure and most of them were severely decompensated.

Of those to whom sucrose was given, three had no cardiovascular disease and the remainder had heart disease. Five of these were compensated at the time of the study and the others were suffering from varying degrees of failure.

Of the total group of cardiac patients, the etiology of the heart disease was hypertension or arteriosclerosis in 20; in five it was rheumatic, and in one it was syphilitic. Five patients were given both sucrose and dextrose.

RESULTS

1. *Effect of Clinical Condition on the Response.*—Although there was considerable variation among different individuals in the results obtained, the cardiac patients tended to respond in the same general way as did the control subjects, and the etiology of the heart disease or the degree or type of heart failure did not apparently influence the response obtained. Because of this and because there were too few patients in each category to permit of statistical analysis, the findings on all subjects are tabulated together.

TABLE I

THE EFFECT OF THE INTRAVENOUS INJECTION OF 100 C.C. OF 50 PER CENT DEXTROSE SOLUTION ON THE VENOUS PRESSURES AND THE PLASMA VOLUME IN TWO CONTROL SUBJECTS AND SEVENTEEN PATIENTS WITH HEART DISEASE

CASE	AGE	DIAGNOSIS	PULMONARY CONGESTION	PERIPHERAL EDEMA	VENOUS PRESSURE ($CM. H_2O$)					PERCENTAGE CHANGE IN PLASMA VOLUME FOLLOWING COMPLETION OF INJECTION*					
					CONTROL LEVEL	AFTER INJECTION									
						1 MIN.	10 MIN.	30 MIN.	60 MIN.	1 MIN.	7-10 MIN.	15 MIN.	30 MIN.	60 MIN.	90 MIN.
1	32	Control	0	0	6.0	12.0	7.5	6.0		+9 (+12)	+11 (+13)	+11 (+6)	+10 (+7)	+3 (−2)	
2	43	Control	0	0	6.5	7.0	7.5	7.0	2.5				(+2)	(+4)	
3	67	Cor. throm.	0	0	5.0	7.0	8.0	8.0	4.5				+5 (−1)	0 (−2)	
4	63	Cor. throm.	+	0	8.0	6.5	3.0	2.0	2.0						
5	52	R. H. D.	0	0	6.5	11.0	8.0	6.5		+17 (+12)	+6 (+10)		+5 (−3)	−1	
6	49	R. H. D.	0	0	4.0	5.5	6.0	6.5	4.0				+3 (+1)		+2 (0)
7	74	Art. scler.	0	0	4.0	4.5	4.0	3.5	3.0				+11 (+7)	+4 (+3)	
8	76	Art. scler.	+	0	0.5	5.0	3.0	1.0	1.0				(+9)		(0)
9	54	Art. scler.	+	0	1.0	3.0	2.0	3.5	−1.0				+13 (+13)		(0)
10	81	Art. scler.	+	+	10.0	17.0		11.0		+13 (+13)	+11 (+16)	+8 (+11)	+11 (+12)	−8 (−3)	
11	75	Art. scler.	0	++	4.0	5.0	4.0			+15 (+14)	+15 (+13)	+12 (+15)	+12 (+13)	+15 (+14)	
12	56	H. H. D. and Art. scler.	0	+++	9.0	11.0	8.5	8.0					(+1)	(0)	
13	60	R. H. D. and Art. scler.	++	+++	9.0	11.0	9.5	8.5	9.0				+7 (+23)	0 (0)	
14	63	H. H. D. and Art. scler.	+	++	8.0	12.0	10.0	9.0	8.0				(+4)		(−2)
15	44	H. H. D.	++	++++	9.5	11.5	9.0	9.0		+8 (+2)	+8 (+3)	+8 (+2)	+1 (+2)		
16	57	H. H. D.	+++	++++	18.0	21.5	20.0	17.5		+7 (+7)	+7 (+8)	+6 (+10)	+6 (+8)		
17	35	R. H. D.	+++	++++	12.5	16.0	13.0			+8 (+5)	+7 (+9)		+3 (+2)		
18	50	H. H. D.	++	++++	12.5	15.5	14.5	12.5					+6 (+6)		+7 (+6)
19	48	R. H. D.	+	++++	14.5	15.0	15.5	13.0	10.0				+13 (+8)		−3 (−5)

Abbreviations: Cor. throm., Coronary thrombosis; R. H. D., rheumatic heart disease; Art. scler., arteriosclerotic heart disease; H. H. D., hypertensive heart disease.

*Figures without parentheses represent percentage changes in plasma volume calculated from plasma protein changes. Figures in parentheses represent percentage changes in plasma volume calculated from hematocrit changes.

TABLE II

THE EFFECT OF THE INTRAVENOUS INJECTION OF 100 C.C. OF 50 PER CENT SUCROSE SOLUTION ON THE VENOUS PRESSURE AND THE PLASMA VOLUME IN THREE CONTROL SUBJECTS AND FOURTEEN PATIENTS WITH HEART DISEASE

CASE	AGE	DIAGNOSIS	PULMONARY CONGESTION	PERIPHERAL EDEMA	VENOUS PRESSURE ($CM. H_2O$)					PERCENTAGE CHANGE IN PLASMA VOLUME FOLLOWING COMPLETION OF INJECTION†					
					CONTROL LEVEL	AFTER INJECTION									
						1 MIN.	10 MIN.	30 MIN.	60 MIN.	1 MIN.	7-10 MIN.	15 MIN.	30 MIN.	60 MIN.	90 MIN.
20	30	Control	0	0	0	2.5	1.5	1.5							
21	64	Control	0	0	2.0	4.0	3.0	2.0	1.0				+19 (+15)		−2 (−6)
22	17	Control	0	0	8.0	9.0	8.5	8.5	7.0				(+10)		(0)
23	61	H. H. D.	0	0	8.0	8.5	9.0	8.0	8.0				−3 (−3)		−4 (0)
24	50	H. H. D.	0	0	6.0	12.0	8.0	9.0					(+4)		
5	52	R. H. D.	0	0	5.0	8.0	5.0	5.0		+17 (+27)	+6 (+19)	+5 (+15)		−1 (+2)	
25	48	*S. H. D.	0	0	1.0	3.0	2.0	−1.0					(+5)		
26	44	H. H. D.	0	0	7.0	9.5	10.0	9.5	7.0				+14 (+8)	+8 (+5)	
9	54	Art. scler.	+	0	0.5	2.5	0.5	0.5					+14 (+3)		−1 (−8)
27	75	Art. scler.	+	+	2.0	6.5	2.0			+13 (+25)	+16 (+27)	+13 (+28)	+10 (+25)	+12 (+12)	
28	76	Art. scler.	++	++	10.5	15.5	12.5	10.5					+8 (+3)	+3 (+2)	
29	51	H. H. D.	++	++	15.0	21.5	17.5								
30	69	H. H. D.	+++	+	10.0	13.0	11.0								
12	56	H. H. D. and Art. scler.	0	+++	16.0	22.0	23.0	21.0	20.0				+4 (+1)		−2 (−4)
31	68	Art. scler.	++	++	0.5	4.5	2.0	1.0		+9 (+12)	+6 (+12)	+4 (+9)	−8 (+6)	−10 (−11)	
18	50	H. H. D.	++	++++	27.0	31.0	28.5	25.0	24.5				+11 (+2)		
15	44	H. H. D.	++	++++	18.5	24.5	20.0	17.0		+3 (+11)	+4 (+8)	+4 (+7)		−8 (+8)	

*Syphilitic heart disease. For other abbreviations see Table I.

†See footnote, Table I.

2. *Dextrose Versus Sucrose.*—Although one might expect on theoretical grounds that a given dose of sucrose might have a more prolonged action than the same amount of dextrose, this was not apparent in the results. The great individual variation in the responses prevented accurate analysis of the results, but in general the effects produced by dextrose and sucrose were similar. Both sucrose and dextrose were administered to five patients. All of them showed a tendency to react in a similar fashion to both substances.

3. *Arterial Blood Pressure and Heart Rate.*—Very little effect was observed on arterial blood pressure or on the heart rate. In four instances either the systolic or diastolic blood pressure, or both, increased from 10 to 22 mm. Hg for a short time following the injection, and in five cases the pressure fell a like amount. In the remainder there was no essential change.

In seven cases the heart rate increased from 8 to 10 beats per minute, and once the increase was 20 beats. These increases lasted, as a rule, a very few minutes following the cessation of injection. The remaining twenty-nine subjects showed pulse rate changes of less than 8 beats per minute, usually none at all.

4. *Venous Pressure.*—There was a tendency for the venous pressure to increase throughout the injection and to start to drop again immediately on its cessation. In one instance there was a slight drop of venous pressure during the injection; in every other case it increased, the rise varying from 0.5 to 7 cm. of water, with an average of 2.6 cm. for those who received dextrose, and 3.5 cm. for those who received sucrose. There was no correlation between these changes and the presence or absence of heart disease or the extent or type of heart failure, with the initial level of the venous pressure, or with the amount of increase in plasma volume. The venous pressure had usually returned to the control level within ten minutes after the injection. In six instances it remained elevated by 2 cm. or more for thirty minutes, but in all but one of these cases it had reached the control level in one hour. In a few instances it fell below the control level at the end of thirty to sixty minutes. This was probably caused largely by increased mental and physical relaxation on the part of the subject, but may in part have been the result of a decrease in blood volume caused by the diuretic effect of the hypertonic injection.

5. *Plasma Volume.*—The maximum dilution of the blood plasma, as estimated from the changes in the plasma proteins, took place almost always within one minute after the end of the injection. This increase in plasma volume was in most instances maintained for about thirty minutes, but had usually disappeared in from sixty to ninety minutes. In three cases only was any appreciable increase in plasma volume maintained for sixty minutes (15, 12, and 8 per cent, respectively). Of the nine patients in whom plasma volume changes were studied at the end

of one minute, the increase ranged from 3 to 17 per cent, with an average of 13 per cent (equivalent to approximately 400 c.c. of fluid). In twenty-two patients the change in plasma volume at the end of thirty minutes was noted. In two cases it had fallen below the control level (–3 and –8 per cent respectively). In the remaining twenty it was still elevated by from 1 to 19 per cent, with an average of 9.1 per cent. The apparent decrease of plasma volume which occurred ten times at the end of sixty to ninety minutes may have been due partly to the experimental error of the technique (maximum experimental error about 4 per cent), but was probably mainly an actual decrease resulting from diuresis caused by the hypertonic solution.

The figures for changes in plasma volume calculated from the hematocrit readings are much less reliable than those obtained from plasma protein changes. Although the absolute figures often did not agree, there was a gross correlation between the two sets of figures.

DISCUSSION

The results obtained are consonant with what could be predicted on theoretical grounds. When 100 c.c. of 50 per cent dextrose or sucrose solution are infused into the circulation, the hypertonic action of the sugar rapidly draws fluid into the circulation so that the total increase in plasma volume may reach 400 to 600 c.c. As the result of this rapid increase in circulating blood volume there is an initial increase in venous pressure. The vascular reservoir, however, rapidly adapts itself to this change in blood volume, so that the venous pressure promptly falls to the control level. At the same time as the increase in plasma volume is occurring, physiologic mechanisms are coming into play which tend to cause fluid to go out of the blood stream; diuresis is usually initiated and the sugar diffuses into the tissue spaces, drawing fluid with it. As a result of a balance of these antagonistic forces, the quantitative extent of which is unpredictable, the increase in plasma volume may be maintained as long as thirty minutes, although the return toward normal frequently starts more quickly. In any case, an increased plasma volume rarely persists for more than one hour.

Since it has been shown experimentally in heart-lung preparations and in anesthetized animals that an increase in venous pressure causes an immediate increase in cardiac output, and since such increase in cardiac output with increase in venous pressure has been shown to occur in humans following large amounts of isotonic or mildly hypertonic intravenous infusions,[12] it is reasonable to infer that an increase in cardiac output often does take place under the conditions of our study.

These findings have certain practical clinical implications. In the first place, we have objective experimental confirmation in man for the clinical belief that hypertonic dextrose and sucrose solutions are of but

very temporary value when given to increase blood volume. It is probable that in states of vascular collapse the increase in plasma volume may be of even shorter duration than in the subjects whom we studied. The administration of 50 per cent dextrose solution to increase blood volume will, however, continue to have clinical usefulness in emergency conditions when acute but temporary vascular collapse can be tided over, or in more severe shock while waiting for the more effective measure of blood transfusion.

As far as can be judged from these results, there is no essential difference between the action of dextrose and that of sucrose on the hemodynamics of the circulation.

It is also clear that the injection intravenously of 100 c.c. of 50 per cent dextrose or sucrose solution within ten minutes produces a distinct strain on the cardiovascular apparatus. Although the absolute burden is apparently no greater in cardiac patients than in normal persons, such patients have much less reserve for such emergencies. No untoward results were encountered in the present series, but it seems not unlikely that in an occasional case such an extra load on the circulation of a patient whose cardiac status is already in precarious balance may result in serious consequences.

The intravenous injection of 100 c.c. of 50 per cent dextrose solution at a rate of 10 c.c. per minute is roughly equivalent in its immediate effect on the cardiovascular system to the infusion of 500 c.c. of a 5 per cent solution of dextrose in physiologic saline at a rate of about 30 to 40 c.c. per minute, or of 1000 c.c. at a somewhat slower rate. The clinical use of 50 per cent dextrose solution is therefore rational when it is desired to produce the effect of a markedly hypertonic solution or to introduce sugar parenterally into the body without giving much fluid, but it is not rational to give it with the idea that less strain on the circulation is produced than would result from the injection of a liter of 5 per cent dextrose solution. When the latter is given slowly there probably results less of an immediate strain.

SUMMARY AND CONCLUSIONS

1. The cardiovascular effects resulting from the intravenous injection of 100 c.c. of a 50 per cent solution of dextrose or sucrose were studied in five control subjects and thirty-one patients with heart disease who had varying degrees of cardiac failure.

2. Slight or no changes in the arterial blood pressure and heart rate occurred.

3. The venous pressure tended to increase moderately during the injection, but began to return toward normal immediately on its completion. The increase ranged from 0.5 to 7 cm. of water, with an average of 2.6 cm. for those who received dextrose and 3.5 for those who received sucrose.

4. The plasma volume increased from 3 to 17 per cent (average, 13 per cent) within a minute of the completion of the injection. The rise persisted a varying period of time, but usually by thirty minutes the plasma volume had begun to fall again and in most cases had reached or fallen below the control level within an hour.

5. No difference in the response was noted which could be correlated with the presence or absence of heart disease, or the etiology, degree, or type, of heart failure.

6. The responses obtained with dextrose and with sucrose were similar.

7. The clinical implications of this study, regarding the efficacy of dextrose and sucrose in increasing blood volume, and particularly as relating to the strain thrown on the circulation by such injections, especially in patients with heart disease, are discussed.

We are indebted to Miss Sophia Simmons for assistance in carrying out the technical procedures, and to Miss Margaret Adams and her associates for performing the plasma protein determinations.

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THE TETRALOGY OF FALLOT

Terminal Sepsis With Crossed Emboli

Richard F. Herndon, M.D., Aloysius Vass, M.D., and
John J. Donovan, M.D.
Springfield, Ill.

THE following case seems worth reporting because of the presence of the typical tetralogy of Fallot in a man 49 years of age, and because crossed or paradoxical emboli occurred during the terminal sepsis.

REPORT OF CASE

An American salesman, 49 years, six months, twenty-two days of age, was seen (by J. J. D.) March 8, 1938, at which time he was complaining of pain in the right lower chest and shortness of breath.

He was born a "blue baby" and grew up a delicate boy who was not expected to live. However, he learned not to hurry and survived two attacks of pneumonia and one of typhoid fever before he was graduated from high school. He was drafted during the war but rejected because of his heart disease. At the age of 28 years he passed a life insurance examination and received a standard policy. He always had a great deal of trouble overcoming respiratory infections. All of the doctors who examined him reported prominence of the left chest, a "bad heart," a slow pulse rate, and a normal blood pressure.

On March 6, 1938, he noticed slight redness and tenderness of the tip of his nose. By March 8 the condition of his nose had grown worse, and at noon he went home and applied moist heat. About 5 P.M. he became feverish and short of breath and developed pain in the right lower chest.

Examination that evening showed a well-developed and well-nourished, acutely ill man, about 50 years old, propped up in bed. His temperature was 103° F., his pulse rate 78, and his respiratory rate 36. The nails and mucous membranes were very cyanotic. The cheeks were flushed and slightly cyanotic. The tip of the nose was swollen, red, and somewhat indurated. The left side of the chest was more prominent than the right. The apex impulse of the heart was visible and palpable in the fifth intercostal space, and was diffuse in character, with its maximum intensity between 2 and 3 cm. outside the nipple. Along the left border of the sternum there was a rough systolic murmur with its maximum intensity in the second and third intercostal spaces. This murmur could also be heard at the apex, but not at the base of the neck. In the right axilla there was a patch of persistent, moist râles, with roughened bronchovesicular breathing. His blood pressure was 112/76. The remainder of the examination revealed nothing abnormal. There was no clubbing of the fingers or toes.

On the following morning he was obviously worse. The cyanosis was more marked and he was listless and drowsy. The swelling of the tip of the nose was less but there was swelling over the bridge of the nose and about the eyes. The hemoglobin was 111 per cent, the erythrocyte count 5,410,000, and the leucocyte count 6,600; 74 per cent of the leucocytes were polymorphonuclears. The urine was normal. By evening the patient's neck was slightly stiff and a few dark petechiae were noted on the left ear. The pulse rate varied between 78 and 110, dropping once to

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54, the respiratory rate varied between 20 and 30, and the temperature between 101° F. and 104° F. On the morning of March 10 he could not be aroused. There were firm edema of the eyelids, chemosis, and left-sided exophthalmos. The entire body was covered with almost black hemorrhagic spots varying from 1 to 3 mm. in diameter. There were marked cervical rigidity, bilateral Kernig signs, and bilateral Babinski signs. A roentgenogram of the chest showed enlargement of the heart and diffuse mottling of the lung fields. The enlargement of the heart was toward the left. The left upper border was quite straight and there was no shadow in the region of the great vessels to the right of the midline. Death occurred at 5:15 P.M., approximately forty-eight hours after the patient went to bed.

Autopsy was performed (by A. V.) three hours after death. Only the thorax and abdomen were opened.

The pleura of the right lower lobe was covered with adherent fibropurulent material and the adjacent pleural cavity contained 300 c.c. of cloudy, flaky fluid. Throughout both lungs there were numerous yellow abscesses, some of which measured as much as 3 or 4 mm. in diameter. Both lower lobes showed confluent bronchopneumonia and, in addition, the right lower lobe contained several recent hemorrhagic infarcts. There was also purulent tracheobronchitis.

The liver weighed 2,500 gm. It presented a typical nutmeg appearance and showed throughout its substance numerous miliary abscesses similar to those found in the lungs. The bile ducts and gall bladder were normal. The spleen weighed 300 gm. Its capsule was thin, its consistency firm, its color bluish-red, and there were miliary abscesses throughout the pulp. The kidneys were normal in size and shape, but on section showed marked cloudy swelling and contained great numbers of miliary abscesses. Similar abscesses were present in the prostate. The other abdominal organs showed only passive hyperemia.

The pericardium was somewhat distended and contained about 50 c.c. of a cloudy, reddish-yellow fluid. The heart was enlarged, weighing 550 gm., and was obliquely egg-shaped. The aorta was large and emerged anteriorly and somewhat to the right, while the pulmonary artery was small and emerged from behind the aorta. The apex was formed predominantly by the right ventricle. There were numerous petechiae and miliary abscesses in the epicardium.

The right auricle was dilated, its endocardium was diffusely thickened, and the pectinated muscles were prominent and thick. It received the inferior and superior venae cavae and the coronary sinus normally. The eustachian and thebesian valves and the limbus were well formed. The fossa ovalis was incompletely closed, leaving anteriorly an elliptically-shaped vertical opening measuring 8 mm. in width. The foramen ovale was patent, admitting a rod 2 cm. in diameter. The tricuspid orifice was of normal size, and its leaflets were well formed, thin, and smooth. Their papillary muscles were hypertrophic. The wall of the right ventricle measured 2 cm. in thickness. Its cavity was considerably larger than that of the left ventricle and it occupied the greater part of the apex. From the posterior upper part of the right ventricle emerged the pulmonary artery. The right ventricle was only incompletely separated from the left by a muscular ridge, which almost completely framed a large opening between the ventricles. This opening was of an obliquely oval shape and measured from 2.5 to 3.5 cm. in diameter. The muscle ridge at its uppermost, arch-shaped portion measured 2.5 cm. in thickness, and at its anterior and lowest portion 2.2 cm. in thickness. It projected into the ventricle from 1.5 to 2 cm. Its uppermost, arch-shaped portion was situated behind and to the right of the aortic orifice and anteriorly and to the left of the pulmonary orifice, extending about 2.5 cm. below the level of their valves. From this arch two limbs extended: a right limb descending along the anterior wall of the ventricle obliquely to the left and ascending again along the posterior wall for a short distance, and a shorter left

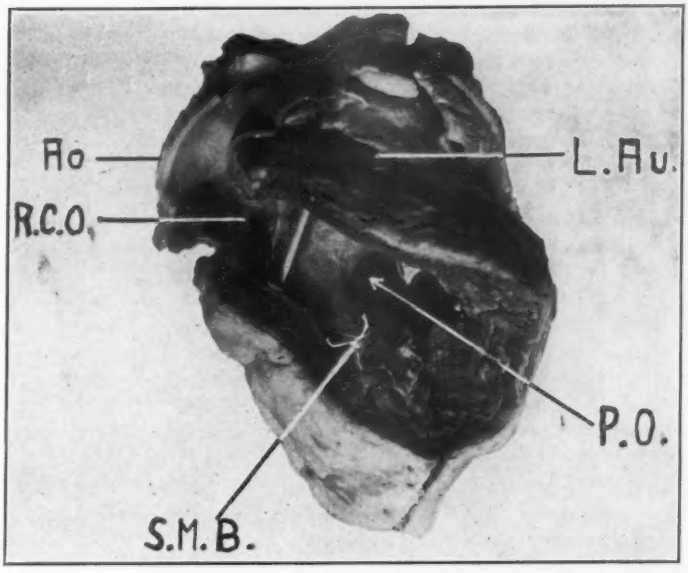

Fig. 1.—Photograph of heart from anterior aspect. Aorta and aortic conus opened. *Ao*, aorta; *L.Au*, left auricle; *R.C.O.*, right coronary orifice; *P.O.*, pulmonary orifice, seen through septal defect; *S.M.B.*, septal muscle bundle.

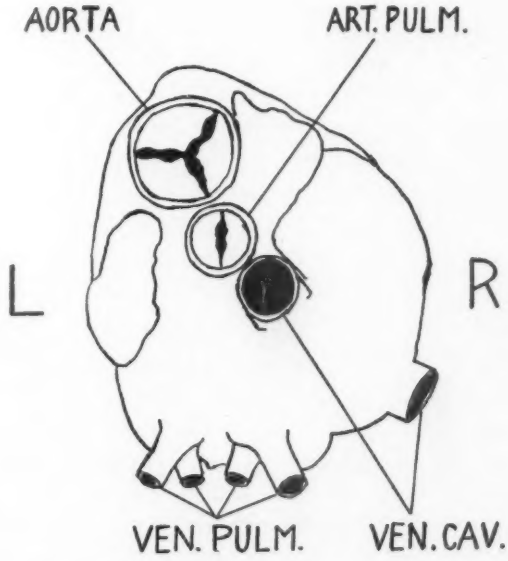

Fig. 2.—Schematic view of the heart from above.

limb which also descended obliquely along the anterior wall almost to the base of the anterior mitral cusp. Posteriorly and to the right of the muscular arch, adjoining and to the right of the aortic cusp of the mitral valve, and to the left of the left cusp of the tricuspid valve, was the pulmonary orifice. It possessed only two cusps, one left and anterior, and one right and posterior. The diameter of the pulmonary orifice measured 1.2 cm., while the greatest width of the elliptical opening between the cusps measured 5 mm. The aortic orifice measured 2.5 cm. in diameter and was situated anteriorly and to the left of the muscular arch. It possessed three cusps, an anterior and a right and left posterior. The noncoronary cusp was situated anteriorly. The ductus arteriosus was obliterated. There was no coarctation of the aorta. The branches of the aortic arch were normal. The mitral orifice was of normal width and its cusps revealed only a few flat, arteriosclerotic plaques. In addition to its normal attachment, the aortic cusp of the mitral valve was also attached to the left posterior portion of the muscular ridge. The wall of the left ventricle measured 2.4 cm. in thickness. The endocardium of the left auricle was slightly, but uniformly, thickened. Numerous petechiae were seen throughout the endocardium. The distribution of the coronary arteries was normal, although they were somewhat rotated to the left. The anterior descending branch of the left and the circumflex branches of both coronary arteries showed distinct thickening of the intima and media and narrowing of their lumina. The myocardium was of a yellowish-red color and revealed on section numerous firm, gray-white streaks and patches and very many yellow miliary abscesses similar to those seen in the other organs.

Anatomic Diagnoses.—Cor triloculare biatriatum; incomplete transposition of the aorta; stenosis of the pulmonary orifice; congenitally bicuspid pulmonic valve; absence of the ventricular septum; hypertrophy of the crista supraventricularis and of the septal and parietal muscle bundles; marked hypertrophy of the heart, particularly of the right ventricle; coronary sclerosis; chronic passive hyperemia of the lung, liver, spleen, etc.; petechiae and miliary abscesses in all organs, including the skin; multiple hemorrhagic infarcts and fibrinopurulent pleuritis of the right lower lobe; bilateral confluent bronchopneumonia.

COMMENT

It seems to us that this man had a furunculosis of the nose, whence the infection spread through the venous channels to produce thrombosis of the cavernous sinus and massive blood stream invasion.[1] The organisms in the various tissues examined after autopsy had the morphologic characteristics of staphylococci. Since an examination of the head was not permitted and cultures were not made, further discussion of this aspect of the case is fruitless.

A precise clinical diagnosis of the nature of the cardiac lesion was not made. When first seen the patient simply said that he had had heart disease since birth, and later he was in no condition to be questioned. He had not liked to talk about his heart and his wife was unfamiliar with his early history, most of which was obtained from an uncle after the patient's death. Without a history of early cyanosis and without clubbing of the fingers, which White and Sprague[2] state is invariably present in the tetralogy of Fallot, we were inclined to believe that he had a combination of interventricular septal defect and patency of the ductus arteriosus. The almost simultaneous ap-

pearance of what seemed to be pulmonary embolic phenomena and what were obviously systemic embolic phenomena required a veno-arterial shunt for their explanation. There was no evidence of sufficient change in the pulmonary circulation to open a previously patent but physiologically closed foramen ovale. We reasoned then that the crossed or paradoxical emboli must have occurred through a septal defect. The history of a slow pulse rate suggested auriculoventricular block and added weight to this idea.

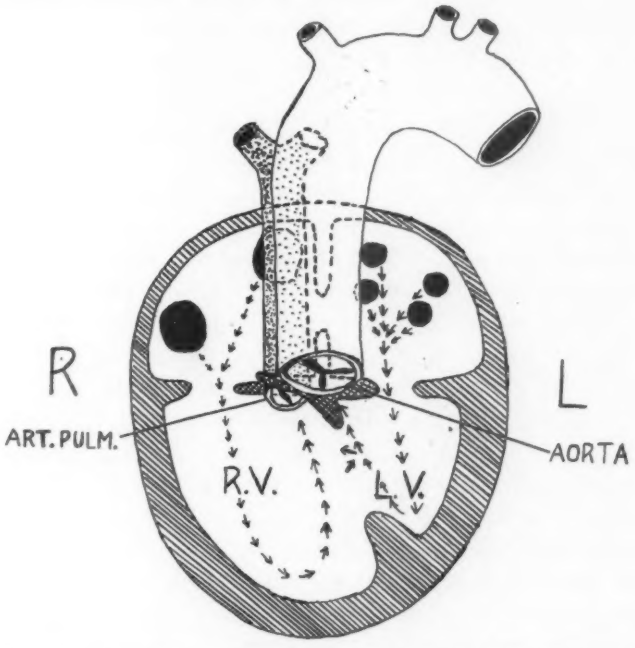

Fig. 3.—Schematic vertical section of the heart. Arrows indicate circulation when no congestive failure is present.

DISCUSSION

Fifty years ago Fallot[3] stated that in congenital heart disease with cyanosis, particularly in adults, the possible malformations are small in number and perfectly definite. His observations have since been amply confirmed and this group is now termed the "tetralogy of Fallot." It consists of: (1) A stenosis or narrowing of the opening of the pulmonary artery at the valve cusps, or of the infundibulum just below them; (2) an interventricular septal defect; (3) dextroposition of the aorta; and (4) hypertrophy of the right ventricle. The course of the blood in such a heart is as follows: The venae cavae empty into the right auricle, from which the blood flows into the right ventricle; at this point the blood stream, obstructed by the narrow pulmonary orifice, only in part enters the pulmonary artery, the remainder going directly into the aortic orifice, which rides over the

interventricular septal defect and so receives blood from both ventricles. The right ventricle hypertrophies to accommodate itself to this increased work and the aorta is larger than normal. In the present case, however, there is evidence both from the history and the examination of the heart that the cardiac circulation was somewhat different. The muscular ridges described were directly in the path of the two streams of blood entering the common ventricle and were so situated that, under favorable hydrodynamic conditions, they would prevent any great mixing of arterial and venous blood (Fig. 3). The absence of cyanosis in similar cases has been noted before,[4] and in this case the mechanism described may have been responsible for the unusually long span of life.

Although Fallot's article, written in 1888, is still thoroughly modern, most of the credit for the present interest in this condition and our ability to recognize it clinically belongs to Paul D. White. White[5] lists five signs which, when they occur together, make the diagnosis of the tetralogy of Fallot practically certain. They are (1) cyanosis of lips, cheeks, ears, fingers, and toes, (2) clubbing of the fingers and toes, (3) a loud systolic murmur heard best in the pulmonary area and the third left intercostal space (at times accompanied by a systolic thrill), (4) marked right axis deviation in the electrocardiogram, and (5), roentgenographically, a sabot-like contour of the heart caused by enlargement of the right ventricle without enlargement of the pulmonary artery. The great vessels are prominent on the right as a result of dextroposition of the aorta, but not to the left because of the small amount of blood passing through the hypoplastic pulmonary artery. Another electrocardiographic finding of some value is auriculoventricular heart block, which might be a sign of congenital malformation of the intraventricular septum.

The congenital nature and interdependence of the anatomic changes noted in this and similar cases have been recognized for years, and a considerable literature dealing with the subject has accumulated. The view of the earliest observers, who believed that fetal endocarditis with subsequent stenosis of the pulmonary orifice and increased pressure in the right ventricle was the cause of the anomalies, has been abandoned. Since Rokitansky's[6] fundamental work it has been quite generally accepted that the pulmonary stenosis and the ventricular septum defect are consequences of the transposition, which in turn is due to abnormal development or rotation of the septum of the common arterial bulb. In 1923, Spitzer[7] suggested a phylogenetic explanation of this process and presented evidence to show that it was a throwback to the period when vertebrates developed pulmonary respiration and two distinct circulations and had a right and left aorta originating from the respective ventricles. In these cases he thought that the phylogenetically atrophying and dormant right aorta

was reopened, while the left aorta was obliterated instead, primarily because of lack of torsion of the large vessels. This theory has since been doubted. Among others, Pernkopf and Wirtinger[8] could find no proof for either an increasing degree of torsion in the higher classes of vertebrates or for the embryonal presence of even a temporary right ventricular aorta in mammals. More recently Lev and Saphir[9] have given what seems to us a more satisfying answer. They believe that the essential process is an abnormal development of the bulboauricular spur which prevents the usual absorption of the arterial bulb into the left ventricle and thus a sufficient degree of normal clockwise rotation around this point. As a result, counter rotation of the unfixed lower end of the arterial bulb takes place, causing a more or less parallel, instead of spirally twisted, position of the aorta and pulmonary artery, and imperfect union or no union between the lower end of the aortic-pulmonary septum and the ventricular septum. They explain the pulmonary stenosis by the presence of a hypertrophic and rotated septal muscle bundle. Our case presents all of the anatomic evidences described by them, namely, the abnormally large bulboauricular spur, the misplaced septal and parietal muscle bundles, and the hypertrophy of both.

The prognosis in this type of malformation of the heart is usually bad. The average age at death in eighty-five cases reported by Abbott[10] was 12½ years. However, the outlook may not always be so discouraging. The oldest patient in Fallot's original series was 36 years of age. Forty years later White and Sprague[2] reported the case of a man who died in his sixtieth year, and in 1936 McGinn and White[5] mentioned a patient who was living at the age of sixty-two. At the present time, our patient seems to be the second oldest of those whose diagnoses have been proved by necropsy. He might have lived much longer but for an intercurrent infection. He had been active and self-supporting until forty-eight hours before his death.

SUMMARY

We have reported a case of congenital heart disease, the tetralogy of Fallot, in a man past 49 years of age who was active and self-supporting until his terminal illness. As far as we can determine, he is the second oldest patient known (autopsy) to have this disease. Death was due to sepsis following furunculosis of the nose and cavernous sinus thrombosis. In the terminal sepsis there were crossed or paradoxical emboli which passed through the septal defect.

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CONTUSION OF THE HEART

Report of a Case With Serial Electrocardiograms

Leslie B. Smith, M.D., and Hilton J. McKeown, M.D.*
Phoenix, Ariz.

A REVIEW of the literature leads one to believe that nonpenetrating wounds of the heart occur rarely. Bright and Beck[1] (1935), in a search of the literature for cases of nonpenetrating wounds of the heart, collected only twelve cases of myocardial contusion in which recovery took place. There were 152 necropsy cases of rupture of the heart, and eleven cases of myocardial failure without rupture in which the diagnosis was established by necropsy. They give an outline of the various ways in which nonpenetrating wounds of the heart were produced.

Beck[2] reported three cases of nonpenetrating wounds of the heart, in one of which the diagnosis was proved by necropsy, and mentioned three additional cases. Kissane[3] has collected and reported fifteen cases illustrating the varying degrees of cardiac contusion which may follow chest injuries. He found that there is usually a relationship between the severity and type of chest injury, but fatal contusion may occur without evidence of trauma to the chest wall. Stromer[4] cites four cases of cardiac contusion, including Hadorn's case, that of a 13-year-old girl who suffered contusion of the heart, in which the electrocardiogram indicated a severe injury of the right side of the myocardium. We have at hand eight cases, other than the one reported here, in which both clinical and electrocardiographic evidence of myocardial damage appeared within twenty-four hours after blows to the chest. Moritz and Atkins[6] have added another case in which the diagnosis was proved by necropsy. Barber[5] mentions six men who had inefficient hearts after severe blows to the chest wall.

The recent experimental studies of Bright and Beck,[1] Moritz and Atkins,[6] and especially of Kissane, Fidler, and Koons[7] have thrown considerable light on this subject; Kissane, and others, injured the hearts of dogs by striking the chest wall over the heart, without opening the chest wall. White and Glendy,[8] in a very comprehensive discussion of "Trauma and Heart Disease," have cited the experimental works of Klubs (1909), Klubs and Strauss (1932), and Schlomka (1934), and have discussed many of the facts and theories pertaining to nonpenetrating wounds of the heart.

Barber[5] states: "Trauma of the heart may result (1) from wounds and direct violence, and (2) from strain of effort . . . direct violence to

*From the Section of Internal Medicine, Lois Grunow Memorial Clinic, Phoenix, Ariz.

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the chest wall may rupture the heart muscle, causing death, or may cause death without obvious heart injury; or it may give rise to the following clinical conditions: (1) pericarditis; (2) angina of effort; (3) a disorder of rhythm; (4) lesions of a valve; (5) contusion of the heart muscle. Strain may result in: (a) a disorder of rhythm; (b) lesions of a valve; (c) primary cardiac overstrain."

It is now well established that trauma may give rise to cardiac contusion, varying in degree from small bruises with slight or no clinical evidence of damage to rupture of the heart wall, even though the blow to the chest may have appeared to be slight. The cardiac impairment following a contusion may clear up completely, or various degrees of impairment may be present for a short time, or for years.

The following case is reported because it demonstrates clearly the possibility of damage to the myocardium from external forces applied to the chest, even though the latter did not leave any evidence of damage to the chest wall. We also believe that this is the first case of trauma to the heart to be reported in which a serial electrocardiographic study was made. It is our opinion that contusions of the heart too frequently are not recognized by physicians, or by our courts and insurance companies.

CASE REPORT*

P. R., a white 17-year-old high school student, had always enjoyed good health. On March 1, 1938, in the course of a routine examination, an electrocardiogram (Fig. 1) and a tereoroentgenogram of his chest were made, both of which were normal.

The patient was injured April 10, 1938, in an automobile collision involving the car he was driving and a truck. It was reported that the patient's chest had struck the left car door sufficiently hard to make an imprint in the door. In this accident he received several lacerations of the scalp and two small puncture wounds about the right elbow. There was only a small visible contusion of the chest, over the right lower ribs anteriorly, with no fractured ribs. The skin wounds were negligible except for a mild, secondary, staphylococcus infection in the puncture wounds, which healed within two weeks.

In the first twenty-four hours he was quite irrational at intervals; however, there were no other evidences of cerebral injury. The hemoglobin was 84 per cent (Sahli). The leucocyte count was 13,800, of which 71 per cent were neutrophilic polymorphonuclear cells, 22 per cent lymphocytes, and 8 per cent monocytes.

During the first forty-eight hours the patient's rectal temperature gradually rose to 102.5° F., and his pulse rate varied from 76 to 100 per minute, being in the upper eighties and nineties most of the time. The blood pressure varied from 100/80 to 136/90. He was irrational at frequent intervals and was very restless. On the third day he began to complain of severe "gas pains," although elimination through the bowels was satisfactory and there were no evidences of abdominal distention. He also complained of some pain in the left anterior chest. On the fourth day the pain in the left anterior chest was quite severe for several hours and restlessness became more marked. The pulse rate ranged from 88 to 100 per minute.

The patient was first seen by one of us (L. B. S.) on the fourth day following the accident. At this time physical and roentgenologic examination revealed noth-

*We are indebted to W. O. Sweek, M.D., and H. G. Williams, M.D., for their cooperation in reporting this case.

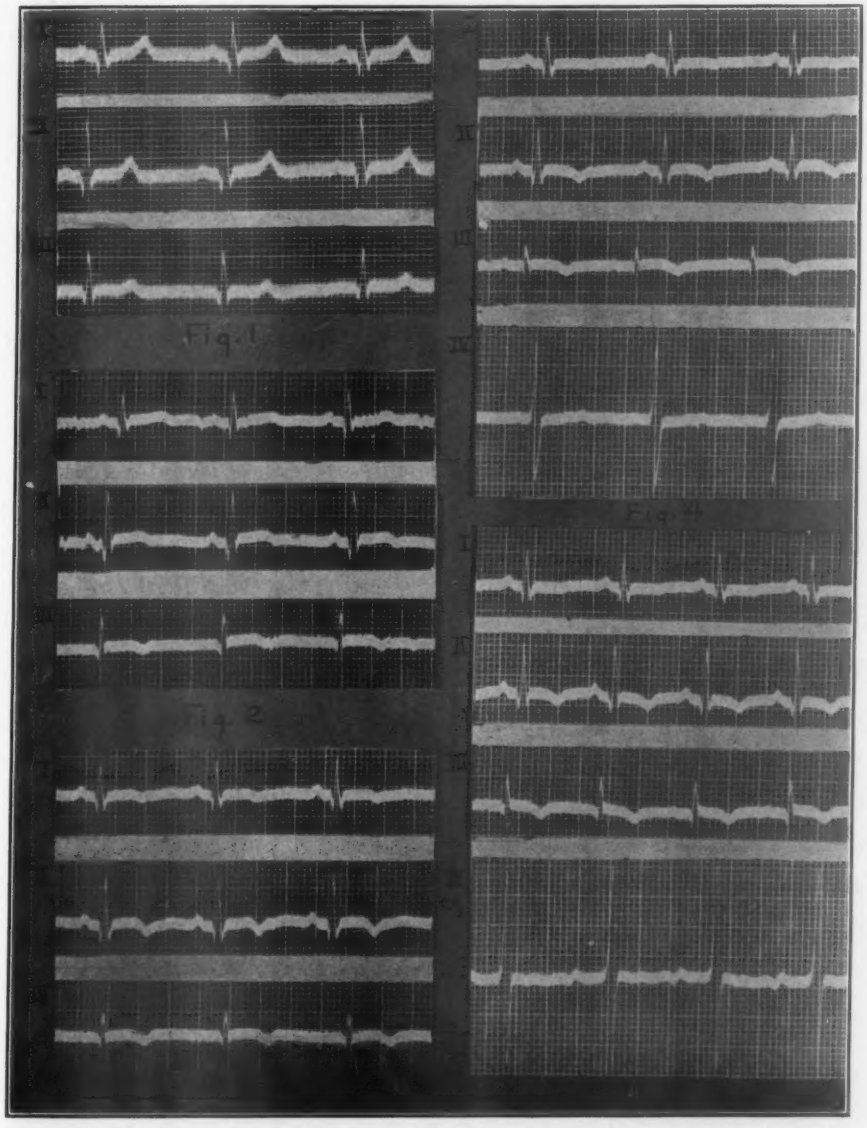

Fig. 1.—Normal. Taken March 1, 1938, 6 weeks prior to accident.

Fig. 2.—Eleven days after the accident and four days after the onset of the precordial pain. QRS, decreased voltage; RS-T, moderately elevated and has a "humped up" effect in all three leads; T_2 and 3, slight negativity. Taken April 21, 1938, eleven days after injury.

Fig. 3.—T_1, slightly negative. T_2 and 3, more negative. April 25, 1938.

Fig. 4.—T_1, isoelectric. T_4 is notched and of lower amplitude than in Lead IV taken six days previously. There has been a slight lessening of the voltage of the QRS in Leads I, II, and III. May 4, 1938.

Fig. 5.—ST_2 sloping downward to an inverted T; Lead III, sloping of ST more marked. T_4, initial negativity. May 12, 1938.

ing abnormal in the lungs. The temperature was 100° F., the pulse rate 100, the rhythm normal, and the blood pressure 100/70. There was no cardiac enlargement. No thrills could be felt. Auscultation revealed that the heart sounds had a peculiar ticktack quality, as if the heart were under strain. At this time it was thought that there was some cardiac involvement. The leucocyte count was 13,200, of which 90 per cent were polymorphonuclear cells, 1 per cent eosinophiles, 1 per cent monocytes, and 8 per cent lymphocytes.

During the next three days the patient's temperature returned to normal. His systolic blood pressure varied from 100 to 110, with a diastolic of 70 to 80. He made occasional reference to discomfort in the region of his heart, but the discomfort in his abdomen had subsided.

On April 17, 1938 (seventh day), following an afternoon of mild physical exertion, he was seized suddenly by a severe pain in the left chest which he described as originating under his left shoulder blade and shooting through to the front of the chest. The pain was continuous, excruciating, and lancinating in character, and was associated with a sensation of breathlessness. He was very apprehensive and restless. Codeine was given for the pain, but it did not begin to lessen for three hours and continued, with varying intensity, for thirty-six hours. During this time he complained of severe pains in the region of second and third left ribs, just lateral to the sternum, and also in the left shoulder and in the left side of his neck, with an occasional extension of the pain to the right side of the neck and right shoulder. Examination of the heart at the time of the onset of the pain and twelve hours later revealed no abnormal findings except that the heart sounds were "labored." The temperature was 99° F., the pulse rate 90 to 100, and the blood pressure 130/70. The leucocyte count was 9,850, of which 62 per cent were polymorphonuclear cells, 33 per cent lymphocytes, 2 per cent eosinophiles, 1 per cent basophiles, and 2 per cent monocytes. Roentgenograms of the chest showed no definite abnormality of the lungs.

Twenty hours after the onset of pain a very definite, loud, pericardial friction rub was heard, of maximum intensity over the second and third left intercostal spaces, just lateral to the sternum. By this time the pain was synchronous with the heart beat, and was aggravated by expiration. At about this time the pain became localized in the region of the base of the heart, with frequent sharp pains in the left shoulder and under the left shoulder blade. The pulse rate was 90 and the temperature 99° F. The blood pressure had dropped to 90/60.

Twelve hours after the first time the pericardial friction rub was heard it disappeared, and was never detected again by frequent examinations. The pain took on an aching character and subsided thirty-six hours after the onset, at which time the pulse rate dropped to 72. The blood pressure remained low during the thirty-six hours of pain, then returned to normal. During the course of the pain the temperature never went above 99.2° F.

A soft, systolic murmur was heard over the second right intercostal space at various times, but not constantly, during the first four weeks.

The patient was kept at rest in bed for six weeks, and was first allowed to be up on May 25, 1938. The remainder of his convalescence was uneventful, except for an occasional attack of dizziness lasting for a few minutes. The temperature, pulse rate, and blood pressure remained normal.

A diagnosis of contusion of the heart was made when the pericardial friction rub appeared, and this was confirmed by the first electrocardiogram (Fig. 2), taken four days after the onset of the precordial pain.

The laboratory findings, other than the electrocardiograms, during the convalescence were as follows: April 25, leucocyte count, 14,100; polymorphonuclears, 80 per cent; lymphocytes, 17 per cent; monocytes, 1 per cent; eosinophiles, 1 per cent;

basophiles, 1 per cent; April 28, sedimentation rate of erythrocytes, 22 mm. in sixty minutes. May 4, leucocyte count, 8,350; polymorphonuclears, 54 per cent; lymphocytes, 35 per cent; eosinophiles, 6 per cent; monocytes, 5 per cent; the blood Kahn and Wassermann reactions were negative. A roentgenogram of the chest showed that both pulmonary fields were clear and free from abnormal shadows; the heart was apparently normal in size, contour and location. May 12, leucocyte count, 6,100; poly-

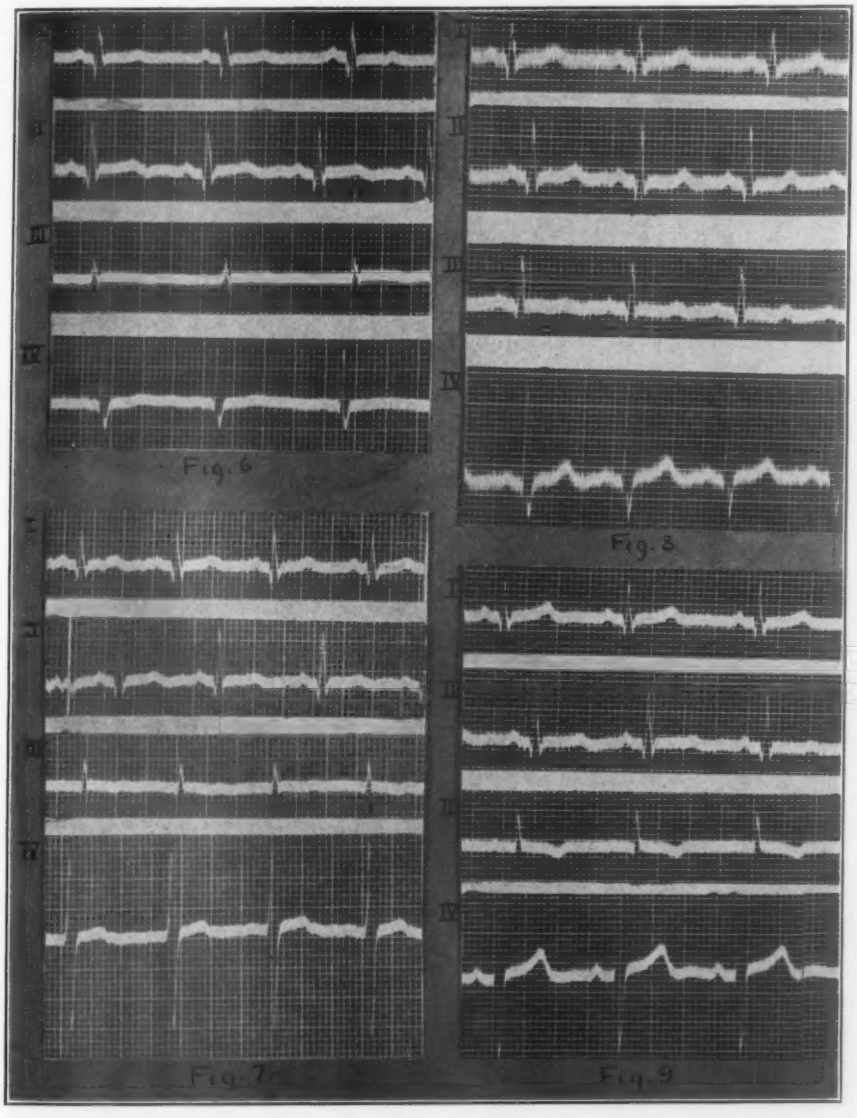

Fig. 6.—Q_1, deeper; T_1, low voltage but positive; T_2, diphasic; T_3, isoelectric; S_4, greatly reduced; T_4, low voltage (S_4, seven days later showed an increase in voltage, but still reduced.) May 19, 1938.

Fig. 7.—T_1, 2, 3, 4, more positive; S_4, increased in voltage. June 1, 1938.

Fig. 8.—Within normal limits, except lessened voltage of S_4. June 13, 1938.

Fig. 9.—T_2, lower voltage. Downward sloping ST_3 with inversion of T_3, RS-T_4 elevated with upward slope. July 28, 1938.

morphonuclears, 56 per cent; lymphocytes, 35 per cent; eosinophiles, 3 per cent; basophiles, 1 per cent; monocytes, 5 per cent; erythrocyte sedimentation rate, 15 mm. in sixty minutes. On June 6 roentgenographic and fluoroscopic examination revealed that no appreciable changes had occurred in the heart since the preceding examination, including that of March 1, 1938, prior to the accident. During convalescence there were no physical or roentgenologic evidences of pericardial effusion. The electrocardiograms are presented below.

Graded physical activities were started on May 25, 1938, and he has been ambulatory since the first week of June, 1938. On July 26, 1938, his physical activities were still limited to short walks. He was unable to indulge in any moderately strenuous physical activities without undue fatigue and persistent increase in pulse rate. Even though the last two electrocardiograms (Figs. 8 and 9) are apparently normal, this patient still had a functional cardiac impairment fifteen weeks following the accident.

He was last examined Sept. 9, 1938, at which time his recovery was almost complete. The pulse rate and blood pressure responses to exercise tests were within normal limits, and radiographic study revealed no abnormalities. The vital capacity was 93 per cent of normal. An electrocardiogram taken on this date shows in Lead III a slight elevation of the RS-T segment, which slopes down to a negative T wave. This RS-T slope, we believe, is a residual effect of the scarring of the myocardium.

A series of twelve electrocardiograms was taken in this case. Three have been omitted because of their similarity to preceding tracings. In the legends, only the serial changes of significance, in sequence, are mentioned; all electrocardiograms were standardized.

DISCUSSION

The serial electrocardiographic changes in this case are similar to those which we have learned to associate with pericarditis.* We believe that if an electrocardiogram had been taken a few days earlier the elevation of the RS-T segment would have been much higher, since it is known that the higher elevations of the RS-T may be transient.

We believe that trauma was the cause of the friction rub in this case. That nonbacterial pericarditis may be caused by trauma is established. Bright and Beck[1] cited two cases from the literature in which death did not occur, and Beck[2] reports another case in which a pericardial friction rub developed. All of these patients had nonpenetrating wounds of the heart. Bright and Beck, in their experimental work, found that fourteen of the seventeen dogs coming to autopsy two to three months after direct trauma to the heart had adhesions between the pericardium and epicardium. Kissane, and co-workers,[7] who found that they could damage the hearts of dogs by striking the chest wall over the heart, state: "The most frequent cardiac lesions were subendocardial and subpericardial hemorrhage . . . pericardial injury and tear with or without free blood in the pericardial sac."

*We wish to thank Dr. Thomas Dry, who saw this patient in consultation two weeks following the accident, and Dr. Arlie R. Barnes, of the Mayo Clinic, who has concurred with our interpretation of the serial electrocardiograms, for their interest in this case.

Infectious pericarditis is rendered unlikely by the fact that the patient had no fever, only a slight leucocytosis, and no appreciable pericardial effusion.

There remain, in our opinion, only the following possibilities, namely, that the accident produced: (1) primary damage to the pericardium or epicardium, (2) primary contusion of the subepicardial myocardium with a secondary plastic pericarditis similar to the nonpurulent pericarditis which frequently follows cardiac infarction, or (3) a combination of these two. The idea that the primary damage was to the myocardium is in keeping with the recently reported findings of Bellet and McMillan[9] concerning the electrocardiographic pattern in pericarditis; they state: "Only when there was demonstrable myocardial damage was deviation of the RS-T segment noted." They interpret their findings, and cite the opinions of others, ". . . as supporting the view that the striking deviation of the RS-T segment associated with certain forms of acute pericarditis is the result of myocardial change that is gross enough to be demonstrable histologically." This view is further supported by the similarity between the electrocardiographic findings in the nonsuppurative pericarditis caused by infarction of the subepicardial myocardium and those in acute bacterial pericarditis.

In their experimental study of contusion of the heart, Moritz and Atkins[6] found that "many of the myocardial changes seen in this series of dogs with cardiac contusion bore striking resemblances to the gross and microscopic changes seen in myocardial infarction in man."

Kissane, and co-workers,[7] found changes similar to those produced by experimental coronary occlusion. The experimental and clinical studies of Bright and Beck[1, 2] indicated that "the most frequent variations from the normal was the production of large T waves and alterations in the Q wave. Frequently there was a high take-off of the T wave; sometimes the T was inverted." Kissane, et al.,[7] found that the most frequent electrocardiographic changes were "in the T waves and RS-T components. . . ." Since contusions may be located in any part of the heart and involve any number of areas, the electrocardiographic changes may be quite bizarre and fit no definite known pattern. It must not be forgotten that trauma may produce serious disturbance in rhythm without any demonstrable lesion.

The diagnosis of contusion of the heart will remain difficult when the patient is in the "coronary age" and recovers. Cardiac trauma may be superimposed on any type of heart disease, and in such cases the role of the trauma may be most difficult to determine. We must recognize that a diseased heart is more vulnerable, and that the disease which exists prior to the trauma is readily aggravated or complicated by it. It is the development of new cardiac signs and symptoms or the accentuation of pre-existing signs or symptoms after trauma that establishes the role of the trauma. The most important diagnostic criteria are enlargement of

the heart as shown by roentgenograms, and serial changes in the QRS, the RS-T segment, or the T waves of the electrocardiogram.

It is our opinion that a diagnosis of traumatic heart disease is justified when a patient receives either a direct or an indirect blow to the chest, or undergoes undue physical strain, or is subjected to other types of external violence, and then develops, without other apparent cause, circulatory embarrassment, or other clinical or electrocardiographic signs of heart disease.

CONCLUSIONS

1. A case of contusion of the heart, with recovery, in a 17-year-old boy, including a serial electrocardiographic study, is presented.

2. Although the electrocardiograms present a pattern that may be associated with pericarditis, in this case the primary damage was to the myocardium and the nonbacterial pericarditis was secondary.

3. Contusion of the myocardium in this case was produced without evidence of any damage to the chest wall.

4. Contusion of the heart is discussed briefly.

5. We believe that cardiac contusions, in this automobile age, are too frequently overlooked.

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CARDIAC ANEURYSM

LOUIS H. BERK, M.D.*
NEW YORK, N. Y.

ALTHOUGH cardiac aneurysms are often found post mortem, very few cases have been reported in which the diagnosis was made clinically and confirmed by necropsy. The reason for the failure to make the diagnosis of cardiac aneurysm is that there are no constant clinical or roentgenologic signs characteristic of the condition. A comparison of the clinical and radiologic signs with the autopsy findings has permitted us to make several observations regarding the diagnosis of cardiac aneurysm.

Cardiac aneurysm is merely a mechanical result of the fibrous transformation of the myocardium. The condition was first studied by Ziegler,[1] and Cohnheim and Schulthess-Rechberg,[2] in 1881, who introduced the concept that the formation of a cardiac aneurysm could be traced to myocardial ischemia. More extensive studies were made by Hall,[3] who in 1903 reported 112 cases and gave a more complete picture of the pathogenesis of such aneurysms. Sternberg,[4] in 1914, wrote a monograph which has since been accepted as the authoritative work on the subject. He predicted that the roentgenologic diagnosis would be possible, described the typical course of aneurysm formation, and brought forth the concept of chronic partial cardiac aneurysm, distinguishing four stages, as follows: (1) the stage of attacks of cardiac pain, often of very short duration; (2) the stage of localized pericarditis at the site of infarction, occasionally producing a pericardial friction rub of only a few hours' duration; (3) the stage of latency, or apparent cure, lasting several weeks to many years; and (4) the stage of advanced myocardial disease, associated with chronic hydrops or leading to rupture.

Kraus,[5] in 1919, first reported the correlation of the post-mortem and roentgenologic findings. Since that time the European literature has contained reports of isolated cases, and a few articles have appeared in the American literature, the most recent being those of Sigler and Schneider,[6] Steel,[7] and Ball.[8]

The development of myocardial aneurysm is logically explained by pathologic changes resulting from a slowly produced obstruction of a coronary artery of the heart by arteriosclerosis, often completed by thrombosis. Such obstruction causes gradual wasting of the cardiac muscle and its replacement by fibrous tissue. In this scarred area the wall of the heart becomes much thinner, and as healing progresses it may

*Bellevue Hospital (Columbia University). First Medical Division, Dr. I. O. Woodruff, Director, and the Department of Laboratories, Dr. D. Symmers, Director.
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become stretched until a saccular dilatation is formed. Thrombi are frequently formed on the inner surface of the sac. If the scar is strong enough to resist the intraventricular pressure, no bulging beyond the line of the epicardium will take place. Such a lesion is termed a partial cardiac aneurysm. If there is a local weakening of the cardiac wall, which then yields to the intracardiac pressure, bulging beyond the line of the epicardium occurs and a chronic cardiac aneurysm is formed. Although aneurysm of the left ventricle may weaken the cardiac wall to the point of yielding, its strength is frequently augmented, and bulging prevented, by the presence of pleuropericardial adhesions, thickening of the epicardium, or thrombus formation within the aneurysmal sac.

The site of cardiac aneurysm is most commonly at the apex of the ventricle, or in the anterior wall immediately above the apex. This marked predilection for the apex is accounted for by the fact that it is the part furthest removed from the blood supply and is the thinnest part of the left ventricle. The larger and older aneurysms naturally involve more of the ventricular wall. The size of these dilatations is rather variable and depends to some extent upon the age of the aneurysm. The causes of death following cardiac aneurysm are: the effects of an embolism derived from a mural thrombus, a severe hemorrhage caused by rupture of the aneurysm, or cardiac failure.

Coronary obstruction is the chief causative factor of cardiac aneurysm, although in a few cases it is reported to have arisen from gummas, ulcerative endocarditis, trauma, or from an abscess or cyst in the heart wall.

CLINICAL FINDINGS

It is a rather curious fact that cardiac aneurysms are rarely manifested by signs peculiar to themselves. Lutembacher[9] stresses the importance of fixation of the apex due to pericardiodiaphragmatic adhesions and localized tenderness over the adhesions. This circumscribed tenderness occurs on digital pressure and persists throughout life. The apex is immobilized by adhesions, as shown by palpation and percussion carried out successively in the right and left decubitus. Displacement of the left border of the heart sometimes simulates displacement of the apex. The precordial pulsations are poorly perceived, although the entire myocardium contracts vigorously.

Frequently, in cases of cardiac aneurysm, the heart beat is feeble, with a diffuse, heaving cardiac impulse, weak heart sounds, and cardiac enlargement. The coexistence of hypertension does not preclude the possibility of cardiac aneurysm. Often there are two palpable cardiac impulses—the true, forceful apex beat, and the heaving contraction of the aneurysmal sac. This has been noted previously by Harvier and Caroli,[10] and by Christian and Frik.[11] Libman[12] stresses the presence of a pulsation, separate and distinct from the apical pulsation and associated with a dull first sound and gallop rhythm, as pathognomonic of aneurysm. In

only one of our cases did we find displacement of the apex beat (Case 1), and in only one case did we find a heaving pulsation over the entire precordium (Case 9). The heart sounds were often distant and muffled, and of poor muscular quality. A soft, apical, systolic murmur was frequently found. There was nothing characteristic about the manifestations of cardiac insufficiency in patients having cardiac aneurysm. However, these manifestations merit our attention because of their abrupt appearance following coronary occlusion and the difficulty with which compensation is re-established. These patients frequently had repeated attacks of congestive failure and pulmonary infarction. These may be the only noteworthy features of cardiac aneurysm. Some patients are surprisingly well, considering their disease. One patient (Case 1) had recurrent attacks of paroxysmal nocturnal dyspnea and pulmonary infarction for a period of six years, and finally succumbed to a massive pulmonary infarct.

RADIOLOGIC FEATURES

In the last four years there has been a considerable increase in the number of cases of aneurysm of the left ventricle in which the aneurysm has been visualized roentgenographically in vivo, and its presence later confirmed by necropsy. Since cardiac aneurysms are found at necropsy in at least 9 per cent of cases of cardiac infarction (Levine,[13] Parkinson and Bedford,[14] Zadek,[15]), we can reasonably expect to find them not infrequently in many cases of coronary thrombosis. Because the clinical manifestations of cardiac aneurysm are rather indefinite, we have come to value the roentgenologic examination as not only helpful but of decisive importance.

Roentgenograms should be made in the anteroposterior and oblique positions, and there should be a fluoroscopic examination. Oblique examination from a series of slightly different angles is indispensable in discovering aneurysms that have developed upon the ventricular surface, especially when they are small in size. Examination in the oblique position offers confirmation that at all points the aneurysm is an integral part of the heart. Measurement of the index of depth, when combined with oblique examination, makes it possible to find the exact location of the aneurysm.

Cardiac aneurysms may be conveniently divided into two general types: (1) a diffuse type with an eccentrically dilated cardiac apex, and (2) a circumscribed dilatation with an oval or angular bulging.

The diffuse form is most frequently encountered. It is marked by an eccentrically dilated cardiac apex with a barely perceptible systolic contraction. The circumscribed type is less frequently seen. It is marked by an oval or angular bulge varying in size, and is most commonly situated at the apex or midportion of the left cardiac border. The degree of pulsation is directly proportional to the size of the aneurysm, and varies inversely with the amount of pericardial thickening and the

presence of adhesions or mural thrombi within the aneurysmal sac (Boller and Pape[16]). Large aneurysms will occasionally show a passive, pulsatory, postsystolic lagging, as in the case reported by Kalisch,[17] and in the case in which Lenk[18] observed no marked pulsation during systole.

Sometimes the hypertrophic myocardium adjacent to the border of the aneurysm appears as a marked prominence with systolic pulsations. This has been mistaken for the aneurysm itself, as in the case of Christian and Frik,[11] in which the bulging was diagnosed as the aneurysm because of its marked pulsation. The necropsy revealed only hypertrophic muscle at that point, while the aneurysm was situated elsewhere.

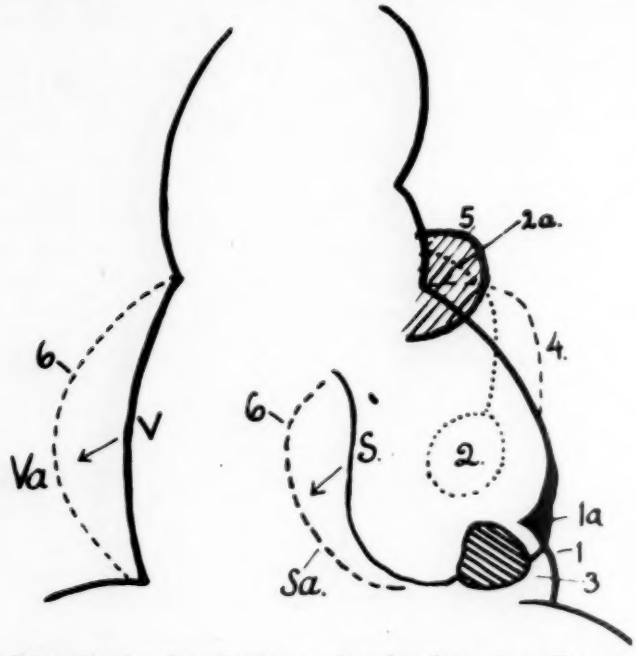


Fig. 1.—Schematic drawing showing various locations of cardiac aneurysms as seen roentgenologically by: Assmann, *1, 1a;* Christian and Frik, *2, 2a;* Jaksch-Wartenhorst, *3*; Kalisch, *4*; Brenner, *5*; Boller, *6*. *V*, Normal contour of right auricle; *Va*, displacement of the right auricular contour toward the right; *S*, normal interventricular septum; *Sa*, aneurysmal bulging of ventricular septum, causing displacement of right side of heart toward right.

Calcification of the aneurysmal wall, which occasionally occurs, appears as a curved line and produces a systolic and sometimes rotatory pulsation, as in the case reported by Jaksch-Wartenhorst.[19] Brenner and Wachner[20] report a case of a large, calcified, saccular aneurysm of the left ventricle near the base, which is a most unusual location. Aneurysms of the ventricular septum can be visualized only if large enough to cause displacement of the right side of the heart toward the right (Boller).

Direct roentgenologic visualization will be impossible if a cardiac aneurysm develops on the diaphragmatic, hepatic, or posterior surface of the heart. The difficulty is increased if the aneurysm does not make

up a part of the left cardiac border, or if, due to adjacent pericardial thickening and adhesions, it does not show bulging or pulsations.

The presence of pleuropericardial adhesions, with immobilization of the apex, which is clearly seen on the fluoroscopic screen, is an indirect corroborative sign of cardiac aneurysm. The cardiodiaphragmatic sinus may be filled with these adhesions. By means of radioscopy it is a simple matter to establish the fact that the site of the localized cardiac pain, which is increased by digital pressure in aneurysm of the left ventricle, corresponds to the location of these adhesions. Measurement of the bisector of the left ventricle reveals that it is uniformly increased. In the absence of concomitant hypertension, this demonstrates bulging of the left ventricular border which would not be apparent without measurement. It is particularly useful in revealing the diffuse type of aneurysm.

REVIEW OF CASES

In this paper we are particularly concerned with the ventricular aneurysms which were found in sixteen patients; the diagnoses were based on clinical and radiologic examination at Bellevue Hospital during the past four years, and on eight autopsies. Of our sixteen patients, eight are still living and under observation (Cases 9 to 16).

We present our cases in two groups. In Table I we report eight cases of cardiac aneurysm in which the patients were examined radiologically during life and the diagnoses later confirmed by necropsy. From the study of this series it would appear that the most important radiologic signs of cardiac aneurysm are the following: (1) diffuse, eccentrically dilated cardiac apex; (2) circumscribed oval or angular bulging of the left ventricular border; (3) presence of pleuropericardial or diaphragmatic adhesions; (4) diminished systolic contraction in the aneurysmal zone; (5) calcification of wall of the sac.

In Table II (Cases 9 to 16) the diagnosis of aneurysm of the left ventricle was based on radiologic examination, together with a history and electrocardiographic findings of coronary occlusion. The examination of these patients, in the light of accepted clinical criteria, has revealed that the following are the most important clinical diagnostic signs: (1) history of coronary occlusion and congestive heart failure; (2) weak first heart sound; (3) cardiac enlargement (these three signs were found in 100 per cent of our cases); (4) diffuse, heaving, precordial impulse (87.5 per cent).

These features, together with the radiologic findings mentioned heretofore, warrant a diagnosis of cardiac aneurysm.

The following signs, though often mentioned in the literature, were less frequently seen in our cases: (1) expansile pulsation between apex and sternum (37.5 per cent); (2) disproportion between the force of the apex beat and the intensity of the heart sounds (50 per cent); (3) fixation of apex and localized precordial tenderness (12.5 per cent).

TABLE I

CASE	SEX	AGE	DIFFUSE ECCENTRICALLY DILATED CARDIAC APEX	CIRCUMSCRIBED OVAL OR ANGULAR BULGING OF LEFT VENTRICULAR BORDER	DIMINISHED SYSTOLIC CONTRACTION OF ANEURYSMAL ZONE	PRESENCE OF PLEURO-PERICARDIAL OR DIAPHRAGMATIC ADHESIONS	CALCIFICATION OF WALL OF THE SAC	AUTOPSY FINDINGS
1	M	37	+	−	+	+	−	Concentric apical aneurysm with calcified mural thrombus covered by pleuropericardial adhesion. Multiple pulmonary, renal, and splenic infarcts.
2	F	67	−	+	+	−	−	Circumscribed saccular aneurysm 8 cm. in diameter in middle of left ventricle extending into interventricular septum.
3	F	70	+	−	+	−	−	Aneurysm of apex of left ventricle 7 cm. in diameter.
4	M	78	+	−	+	+	−	Diffuse dilatation of left ventricle near apex and posterior to interventricular septum extending upward 8 cm., filled with calcified mural thrombus.
5	M	69	−	+	−	−	−	Ruptured saccular aneurysm of left ventricle 4 cm. in diameter extending to within 2 cm. of apex. Sac partially filled with soft thrombus.
6	M	51	−	+	+	−	−	Saccular aneurysm of apex.
7	M	60	+	−	+	−	−	Diffuse bulging of anterior wall of left ventricle extending into the interventricular septum; pericardial adhesions.
8	M	49	+	−	+	−	−	Aneurysmal dilatation of left ventricle in region of apex and interventricular septum.

TABLE II

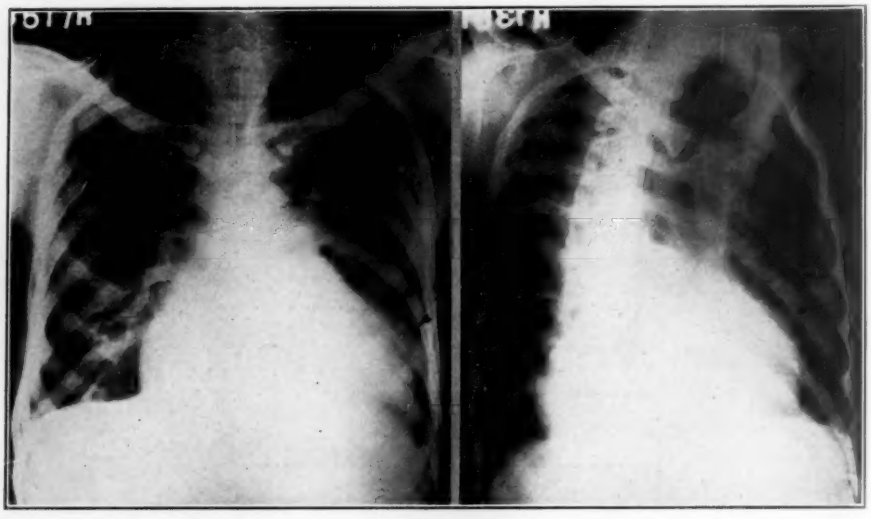
CASE	SEX	AGE	HISTORY		CLINICAL SIGNS								RADIOLOGIC SIGNS					
			HISTORY OF CORONARY THROMBOSIS	PRESENCE OF CONGESTIVE HEART FAILURE	DIFFUSE HEAVING PRECORDIAL IMPULSE	PULSATION BETWEEN STERNUM AND APEX	DISTANT FIRST HEART SOUND	FIXATION OF APEX ON PERCUSSION IN LATERAL DECUBITUS	TENDERNESS OVER APEX	DISPROPORTION BETWEEN FORCE OF APEX IMPULSE AND INTENSITY OF HEART SOUND	CARDIAC ENLARGEMENT	PRESENCE OR ABSENCE OF HYPERTENSION	EKG CHANGES	DIFFUSE ECCENTRICALLY DILATED CARDIAC APEX	CIRCUMSCRIBED OVAL OR ANGULAR BULGING OF LEFT VENTRICULAR BORDER	DIMINISHED SYSTOLIC CONTRACTION OF ANEURYSMAL ZONE	PRESENCE OF PLEUROPERICARDIAL ADHESIONS	CALCIFICATION OF WALLS OF THE SAC	BISECTOR OF LEFT VENTRICLE (NORMALLY 1.2 TO 1.8 CM.)
9	F	43	+	+	+	+	+	-	+	+	+	+	BBB*	+	+	+	-	3.8
10	M	55	+	+	-	+	+	-	-	+	+	-	T_1-T_2 type	-	-	+	-	2.2
11	M	74	+	+	+	-	+	+	-	+	+	-	BBB	+	+	+	-	2.4
12	M	51	+	+	+	+	+	-	-	-	+	+	BBB	-	+	+	-	2.6
13	M	47	+	+	+	-	+	-	-	-	+	+	T_1-T_2 type	+	+	+	-	2.0
14	M	55	+	+	+	-	+	-	-	+	+	+	BBB	+	+	+	-	2.8
15	M	47	+	+	-	-	+	-	-	+	+	+	T_1-T_2 type	+	+	+	-	2.0
16	M	70	+	+	+	+	+	-	-	+	+	+	T_1-T_2 type	+	+	+	-	2.2

*Bundle branch block.

It must be understood, however, that the absence of any one or even all of these signs does not necessarily eliminate the possibility of cardiac aneurysm. It may be concluded from the above evidence that in any given case of cardiac aneurysm there will be sufficient clinical features to suggest the diagnosis. The roentgenographic examination will confirm or contradict this impression.

CASE REPORTS

The following four cases illustrate the two types of cardiac aneurysm. Cases 1 and 9 are of the diffuse and eccentrically dilated type. Cases 2 and 10 are of the circumscribed type. In the first and second cases, taken from Table I, the diagnosis was confirmed by necropsy.



A. *B.*

Fig. 2.—*A*, Case 1. Teleoroentgenogram showing enlargement of the heart to the left, with blunting of the apex. Typical of diffuse cardiac aneurysm. *B*, Case 1. Right anterior oblique roentgenogram, revealing a diffuse bulge of the left ventricular border with typical angulation. Presence of aneurysm confirmed by necropsy.

CASE 1.—R. M., a 37-year-old colored man, had been admitted to Bellevue Hospital seven times with congestive heart failure. On his first admission (Nov. 1, 1933), patient complained of substernal pain, shortness of breath, edema of both ankles, and swelling of the abdomen. Physical examination revealed a markedly enlarged heart with a diffuse precordial pulsation and a systolic murmur over apex and base. Normal sinus rhythm was present. The blood pressure was 124/96. The edge of the liver was tender and the liver was pulsating. During his stay in hospital the patient developed recurrent right-sided hydrothorax with expectoration of bloodtinged sputum. After each admission the patient improved with bed rest, digitalis, and salyrgan injections, and was discharged. At short intervals, however, increased dyspnea recurred with mild congestive failure, necessitating his readmittance to hospital. He was admitted to the hospital four times for pulmonary infarctions with expectoration of blood. The electrocardiogram revealed normal sinus rhythm, myocardial changes associated with coronary artery disease, and low voltage.

Roentgenologic examination of the heart (June 8, 1936) revealed a diffuse rounding of the left ventricle, with blunting of the apex. The roentgenogram taken in the right oblique position showed an aneurysmal bulge on the anterior heart border, with typical angulation of the left ventricular contour (Fig. 2*A* and *B*). The left auricular appendage was accentuated, the left auricle was enlarged, and the esophagus was displaced. There were fibrosis and congestion of both lung fields with obliteration of the cardiophrenic angle. Fluoroscopy showed pleuropericardial adhesions about the apex and over the right diaphragmatic dome.

Necropsy, performed Feb. 13, 1938, showed a large aneurysmal sac projecting through the anterior wall of the left ventricle, lined by a partially organized clot containing calcium. The myocardium in the apical region showed thinning and marked scarring. The wall of the sac and its overlying tissue covered an area about 3 by 1.5 cm. The anterior descending branch of the left coronary artery was completely occluded and calcified. The right coronary artery showed less thickening than the left, and no occlusion was found.

There was an adherent pleurisy of the right and left lower lobes, with infarction of the right middle lobe. A healed splenic infarct, multiple healed kidney infarcts, and cardiac cirrhosis of the liver were also found.

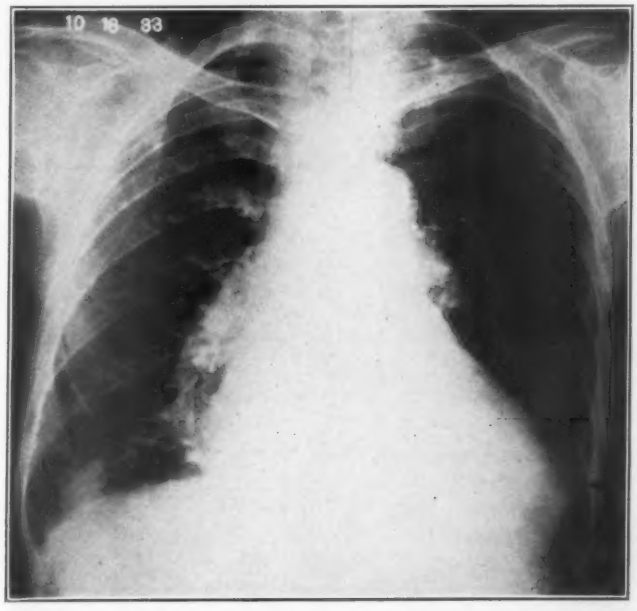


Fig. 3.—Case 2. A circumscribed cardiac aneurysm of the left apex. Presence of aneurysm confirmed by necropsy.

Case 2.—M. W., a 67-year-old woman, first began to notice shortness of breath and weakness in March, 1933, followed by swelling of the feet and ankles. Physical examination on admission revealed an enlarged heart. The point of maximal impulse was in the fifth intercostal space 12 cm. from the midsternal line. The heart sounds at the apex were distant; normal sinus rhythm was present. The aortic second sound was louder than the pulmonic second. The blood pressure was 128/90. There was marked thickening of the peripheral arteries. The liver was just palpable and was tender. There was slight pretibial edema. The patient grew progressively worse and died Nov. 1, 1933.

The electrocardiogram showed normal sinus rhythm and marked left ventricular preponderance; there were no changes suggestive of myocardial damage. Roentgenologic examination showed considerable enlargement of the heart to the left, with a small, circumscribed outward bulging of the apex. This would suggest a circumscribed cardiac aneurysm of the left side of the apex (Fig. 3).

Necropsy revealed an old myocardial infarction with a small circumscribed aneurysm of the apex of the left ventricle. The anterior descending branch of the left coronary artery was occluded by an organized and partially calcified thrombus. The myocardium was hypertrophic and reddish brown in color, except for an area, 8 cm. in diameter, in the interventricular septum. There the myocardium was practically replaced by fibrous tissue, and the thickness of the wall was only about 4 mm. This area bulged into the right ventricle. The endocardium over this area was smooth and thickened. No thrombus formation was seen.

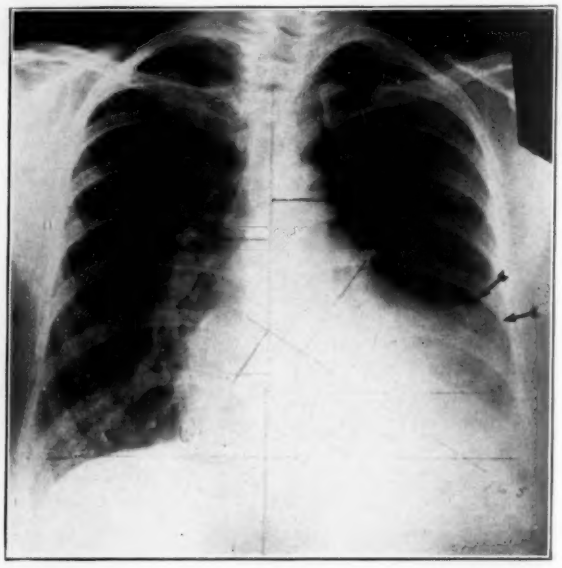


Fig. 4.—Case 9. Teleoroentgenogram showing a marked bulge of the outer portion of the left ventricle, with sharp angulation of the left border, giving the heart a rectangular appearance.

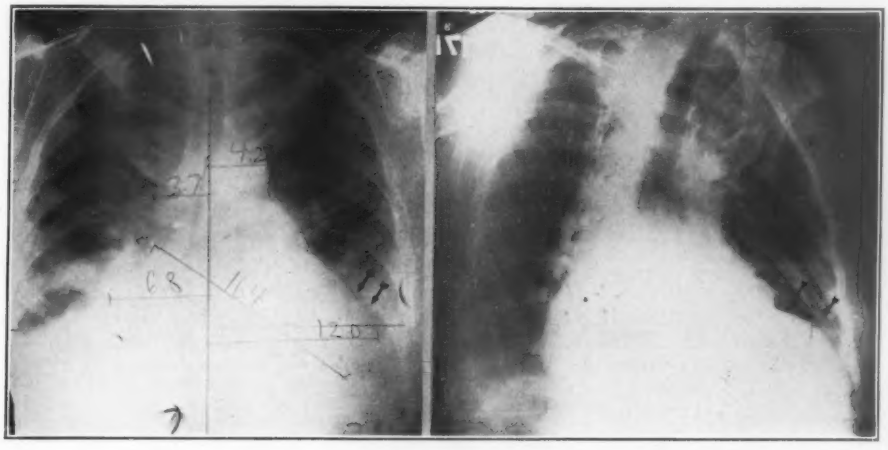
Case 9.—L. H., a 43-year-old woman, was admitted to Bellevue Hospital three times. She had diabetes mellitus, but on her third admission (Nov. 25, 1934) she complained of a prolonged attack of severe pain across the middle of the chest, radiating to both arms.

Physical examination revealed that the heart was markedly enlarged to the left, with a diffuse precordial pulsation extending to the midaxillary line in the fifth intercostal space. In addition to the apical impulse in that space, there was a sharply localized impulse in the fourth intercostal space 14 cm. from the midsternal line. The first heart sound was muffled and had lost its muscular quality. There were a few moist râles in both bases, and tenderness over the liver. The electrocardiogram revealed normal sinus rhythm with left bundle branch block.

Roentgenologic examination disclosed gross enlargement of the heart to the left, mainly of the left ventricle, with sharp angulation of the left border, giving the heart a rectangular appearance. The maximum transverse diameter was 15.1 cm., the total length 16.5, the broad diameter 11.5, and the width of the pulmonary fields 25 cm. (Fig. 4).

CASE 10.—E. T., a 51-year-old man, was admitted to Bellevue Hospital Aug. 22, 1938. There was a history of severe substernal pain radiating to the left arm lasting several hours. This attack had occurred four months prior to the patient's admission to hospital. The attack was followed by gradual swelling of the feet and shortness of breath.

Physical examination on admission revealed an orthopneic, dyspneic, obese man, acutely ill. The heart was markedly enlarged. There was a feeble apex beat in the fifth intercostal space at the anterior axillary line. Fairly well-localized pain was present over this area; the heart sounds were muffled and distant, with a suggestion of gallop rhythm. Normal sinus rhythm was present, with an occasional extrasystole. The blood pressure was 90/60. Subcrepitant râles were heard over both lower lobes. The liver was four fingerbreadths below the costal margin, and there was slight pretibial edema. The electrocardiogram revealed inversion of T_1 and T_2, suggesting anterior wall infarction.



A. *B.*

Fig. 5.—*A*, Case 10. Teleoroentgenogram showing enlargement of the heart to the left, with a diffuse cardiac aneurysm (note *B*). *B*, Left oblique roentgenogram, showing heart seen in *A*. Note deep groove, and ledging of the midportion of the left ventricular border.

Roentgenologic examination revealed gross enlargement of the heart and blunting of the apex. There was congestion of both lung fields with prominence of the aortic knob. In the left oblique view there was marked ledging of the middle left ventricular border, as seen in Fig. 5. Fluoroscopic examination disclosed an enlarged heart with rounded apex and diminished amplitude of the pulsation of the left ventricle. A marked wedge-shaped indentation in the middle of the left cardiac border was observed on rotating the patient to the left oblique position (Fig. 5 *A* and *B*).

SUMMARY

1. The clinical and radiologic features of sixteen cases of cardiac aneurysm are described, in eight of which the diagnosis was confirmed by necropsy.

2. The necropsy observations have been correlated with the radiologic findings; the most constant of the radiologic signs were used as diagnostic criteria.

3. The significant clinical features are shown to be: a history of coronary thrombosis with congestive failure; cardiac enlargement; weak

first heart sound; and a diffuse heaving precordial impulse. Disproportion between the force of the apex beat and the intensity of the heart sounds, an expansile pulsation between the apex and the sternum, and localized precordial tenderness with fixation of the apex are presented as rare, but strongly suggestive, signs.

4. Since cardiac aneurysm is merely the mechanical result of fibrous transformation of the myocardium following coronary thrombosis, radiologic evidence of its presence can be seen in changes in the size, shape, and contour of the heart.

5. There are two types of cardiac aneurysm: (1) the diffuse, eccentric dilatation of the cardiac apex, and (2) the circumscribed bulge.

6. Since cardiac aneurysm is encountered in at least 9 per cent of all cases of coronary thrombosis, constant vigilance together with a knowledge of its clinical and radiologic manifestations will increase the frequency with which the condition is diagnosed during life.

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THE THERMAL REFLEX VASODILATATION TEST IN PERIPHERAL VASCULAR DISEASE

GAMLIEL SALAND, M.D., CHARLES KLEIN, M.D., AND
HERMAN ZURROW, M.D.
NEW YORK, N. Y.

ATTENTION has already been called to the value of a vasodilating test in the study of the peripheral vascular diseases. As early as 1883, Mitchell[1] showed that paralysis of a peripheral nerve trunk by cold is associated with hyperthermia in the anesthetic zone. In 1926, Brown[2] obtained vasodilatation by means of the intravenous administration of typhoid vaccine. In May, 1930, White,[3] and Brill and Lawrence,[4] at the same time, but working independently, showed that spinal anesthesia caused an increase in the surface temperature of the feet.

Scott and Morton,[5] in June, 1930, found that general anesthesia gave the same complete obliteration of vasoconstriction. Again, in October, 1931, Scott and Morton[6] injected the posterior tibial nerve to differentiate arterial spasm from organic obstruction.

Sir Thomas Lewis,[7] in 1929, used heat to induce peripheral reflex vasodilatation.

In 1932, Gibbon and Landis[8] observed that immersing the hands and forearms in warm water produced vasodilatation in the lower extremities of six normal persons, and that the temperature of the toes began to rise in fifteen minutes and rose to over 31.5° C. in all cases. In November, 1933, Landis and Gibbon[9] studied patients with peripheral vascular disease, and found that the immersion test compared favorably with other methods of vasodilatation.

The reason for using a vasodilatation test is obvious to all workers in the field of vascular diseases. It is a known fact that arterial spasm can simulate every symptom and physical sign of organic obstruction, such as cold feet, painful extremities, claudication, absent pulsations, rubor, and pallor. It is also known that instrumental aids, such as oscillometric tracings and intra-arterial thorotrast injections, reveal only the presence or absence of obstruction, but when obstruction is demonstrated, these tests do not differentiate spasm from organic block.

In our work we followed the method of Gibbon and Landis for the following reasons: (1) it eliminated the danger of trauma to the vessels, (2) injection carried with it the risk of infection, and (3) many patients objected to an injection.

From the department of peripheral vascular diseases, Bronx Hospital, New York.
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We are reporting results on seventy-three patients who had symptoms of peripheral vascular disease. Each patient had a complete history and physical examination, urine examination, blood counts, and blood Wassermann and Kahn tests. When necessary, a chemical examination of the blood was made and electrocardiograms taken. The local examination was supplemented by recorded oscillometric tracings at the knee and ankle, roentgenograms of the peripheral vessels and, finally, by the thermal test.

Just prior to doing the thermal test the case was classified as either one of organic, functional, or no peripheral vascular disease. However, in this report we divided our cases into two main groups, namely, Group I, cases in which the temperature of the big toe rose to 30.5° C. or over, and, Group II, cases in which the temperature of the big toe failed to rise to 30.5° C.

Technique of the Test.—We followed the technique of Gibbon and Landis.[8] We tried to keep the room temperature as constant as possible, and avoided all drafts. The subject, whose rectal temperature was not over 100° F., was seated on a chair with the lower extremities in the horizontal position, exposed from above the knees. The readings were taken with the Taylor Dermatherm on the dorsum of the big toe at the base of the nail. Both extremities were examined. Readings were taken until the temperature of the big toe was the lowest possible at the room temperature prevailing. We tried to have the initial temperature of the big toe 26° C., or lower; this frequently necessitated an exposure of one-half hour or longer. Both forearms and hands were then immersed in water at 45° C., and readings from the big toes were taken with the dermatherm every three minutes for a period of one-half hour. At the time of immersion the patient's body was covered with wool blankets. Rectal temperatures were taken at the end of each test. Normally, a significant rise in toe temperature should occur in fifteen minutes, and at the end of thirty minutes should reach the absolute value of 30.5° C., or over.

For the sake of simplicity in following our results we have reported the findings in only one extremity, and we have selected the extremity showing the lower reading.

Rationale of the Thermal Test.—Immersion of the forearms in water at 45° C. tends to raise the temperature of the blood in those limbs. When the warmer venous blood reaches the medulla it affects the vasomotor center, inducing a reduction of vasomotor tone in an attempt to maintain constant body temperature.

Group I (A).—Cases in which the temperature did not rise to 30.5° C. (initial temperature of the big toe 26.0° C., or lower). In this group there were forty-four cases, including thirty-three of arteriosclerosis obliterans with or without ulceration, infection, or gangrene, five cases of thromboangiitis obliterans, one of scleroderma, one of thrombophlebitis with arteritis, one of vasospasm, and three in which no vascular disease was diagnosed. Forty subjects in this series failed to show an elevation of the temperature of the big toe to 30.5° C. In other words, the thermal test gave corroborative evidence of organic obstruction in forty out of forty-four cases, or 91 per cent. However, four patients who were re-

garded as having no organic obstruction also failed to show a rise to the absolute value of 30.5° C.

Group I (B).—Cases in which the temperature did not rise to 30.5° C. (initial temperature of the big toe above 26.0° C.). This group comprised eleven cases of arteriosclerosis obliterans, with or without ulceration, infection or gangrene. In no instance, in spite of the fact that the initial temperature of the big toe was over 26.0° C., was there a rise to 30.5° C. In other words, there was 100 per cent corroboration of the presence of organic vascular disease in this series. The percentage corroboration of the test for the entire Group I was 93 per cent.

Group II (A).—Cases in which the temperature rose to 30.5° C., or over (initial temperature of the big toe 26.0° C., or lower). In this group there were seven cases, in all of which the diagnosis of no peripheral vascular involvement had been made. In all of these cases the temperature of the big toe rose as it would in a normal individual, a 100 per cent corroboration by the thermal test of the fact that in these cases there was no organic obstruction.

Group II (B).—Cases in which the temperature rose to 30.5° C., or over (initial temperature of the big toe above 26.0° C.). In this group there were eleven cases, including two of arteriosclerosis obliterans, one of Raynaud's disease, and eight in which no peripheral vascular disease was diagnosed. The patient with Raynaud's disease had no involvement of the lower extremities, and for the purpose of this article may be grouped with the nine normal subjects. All eleven subjects showed a rise in the temperature of the big toe to 30.5° C. In this group, therefore, the thermal test corroborated the clinical findings in 82 per cent of the cases.

TABLE I

SUMMARY OF THERMAL RESPONSE

DIAGNOSIS	TOTAL NO.	SURFACE TEMPERATURE OF BIG TOE		PER CENT CORROBORATION OF DIAGNOSIS BY THERMAL TEST
		ROSE TO 30.5° C.	FAILED TO RISE TO 30.5° C.	
Organic occlusive arterial disease	53	2	51	96
No peripheral vascular disease	20	16	4	80

DISCUSSION

We have studied seventy-three patients who were sent to our clinic for diagnostic and therapeutic purposes. We did a vasodilatation test in each case in addition to using other known methods of proving the presence or absence of organic obstruction. We have shown that in cases in which there was no evidence of vascular disease the thermal test was normal in 80 per cent, and that in those in which a diagnosis of organic obstruction had been made the thermal test showed that the surface

temperature of the big toe failed to rise to 30.5° C. in 96 per cent of the cases.

In two cases in which a clinical diagnosis of arteriosclerosis obliterans was made, the response to the thermal test was normal. One must assume in such cases that either there is an element of spasm, and that this spasm is relaxed by vasodilatation, or that there exists a sufficient collateral blood supply to allow enough blood to reach the extremity and warm it. If the latter should be true, then it is rational to assume that this test can be used to measure the effect of any kind of therapy used in peripheral vascular disease.

CONCLUSION

The thermal reflex vasodilatation test is a safe and simple method to differentiate organic from nonorganic obstruction of the peripheral arterial system, and also to determine whether or not the blood supply to a limb is sufficient.

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THE INTERPRETATION OF THE U WAVE OF THE ELECTROCARDIOGRAM*

L. H. NAHUM, M.D., AND H. E. HOFF, M.D.†
NEW HAVEN, CONN.

THE U wave was first observed by Einthoven in the electrocardiogram of a patient with myocardial disease and was attributed to the abnormal duration of ventricular systole in a damaged heart.[1] Subsequently, Einthoven found the U wave in electrocardiograms of normal subjects, and concluded that the wave indicated persistence of contraction in some fibers during early diastole.[2] Lewis and Gilder[3] recognized this summit in thirty-two cases out of forty-nine in Lead I, in forty-four out of forty-nine in Lead II, and in fourteen out of thirty in Lead III. By means of simultaneous electrocardiographic and carotid pulse curves, they calculated that the U wave occurred almost, if not entirely, after the closure of the semilunar valves. Soon afterward, Hering[4] suggested that the U wave may be caused by electrical activity in the great arteries.

Since then the possibility that the U wave may represent a phase of electrical activity of the ventricle has been disregarded, and the concept that electrical and mechanical events in the ventricle terminate more or less simultaneously at the end of the T wave has developed. Recently, however, the work of Erlanger and Gasser[5] on nerve has revealed the existence of after-potentials whose duration far exceeds the period of excitation accompanying propagation of the impulse; such potentials are associated with the various phases of the recovery process. Factors which influence metabolism and affect recovery are found to have a profound influence on these after-potentials. A phase of recovery particularly influenced in this manner is the supernormal period which follows the relative refractory phase and is associated with the negative after-potential.

The supernormal period has in the past been found infrequently in the frog's ventricle,[6, 7] the conduction system,[8, 9] and the pacemaker.[10] In a previous communication we have demonstrated that it is invariably present in the ventricle of the cat under amytal anesthesia, and have found that when a U wave is present the supernormal period coincides with it.[11] We concluded that the U wave is to be considered a part of the ventricular complex, representing the location of the supernormal period. The present study was undertaken to determine whether the U wave and

*Aided by a grant from the Fluid Research Funds, Yale University School of Medicine. We are indebted to the Department of Cardiology, Grace Hospital, New Haven, for part of the clinical material presented here.

†Laboratory of Physiology, Yale University School of Medicine, New Haven.

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the supernormal phase coincide in other mammals, and to ascertain how this interpretation of the U wave may contribute to our understanding of the ventricular electrocardiogram in man.

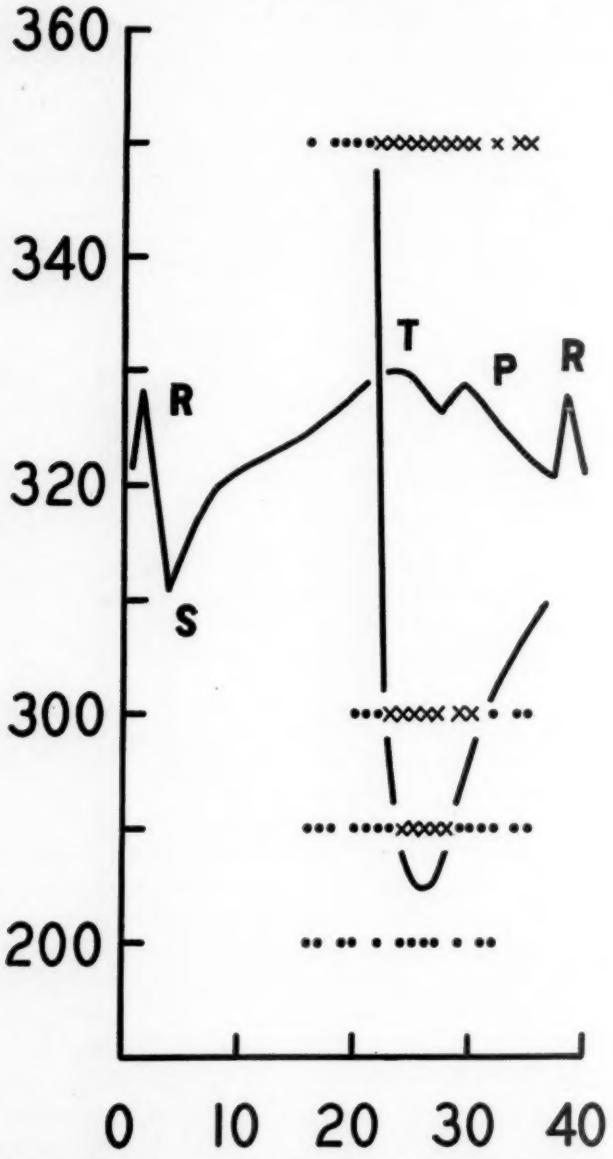

Fig. 1.—Chimpanzee Becky, 32 kg. Sodium amytal anesthesia (60 mg. per kg.). Heart exposed through sternum and anterior mediastinum without opening pleural cavities. Point stimulated on anterior surface of left ventricle. Ordinates, peak voltage of induction shocks. Abscissae, time in hundredths of a second. Crosses represent shocks which evoked extrasystoles, and dots ineffective shocks. From 0.22 to 0.30 after the onset of R, shocks are effective at strengths which later in the cycle fail to evoke a response. This is the supernormal period. A scale drawing of a single electrocardiographic complex from Lead II shows that the supernormal phase occurs here during the descending portion of T.

EXPERIMENTAL STUDIES

The recovery cycle of the hearts of six dogs and one adult chimpanzee was studied by the method previously described.[11] The heart was exposed and the pericardium sewed to the chest wall in such a manner that the pleural cavities were closed, and the animal could breathe. A silver hook was inserted into the epicardium over the ventricle and paired with an anal electrode, permitting induction shocks to be delivered to the heart. By varying the strength of these shocks, the excitability of the heart was determined throughout the cycle. The usual absolute refractory period was determined, when no stimulus of whatever strength could evoke an extrasystole. This was followed by the relative refractory period, during which shocks were able to elicit a response provided they were of greater intensity than those which were effective during late diastole. Subsequent to this the excitability of the heart increased, so that a shock too weak to evoke a response later in diastole now produced an extrasystole. This period is recognized as the supernormal period, and lasted from 0.10 to 0.15 second. It appeared in all animals anesthetized with sodium amytal, but was not detectable when morphine was employed as the analgesic.

In the chimpanzee (Fig. 1) and in one dog the supernormal period was found on the down stroke of the T wave, and a U wave was not detected. In two other dogs U waves were seen, and in these animals the supernormal period fell on the U wave (Fig. 2). In one of these experiments the supernormal period was inconstant, appearing and disappearing within a few beats, but without any recognizable relation to respiration. These experiments confirm the observations on cats, and establish the existence of a supernormal phase in the ventricles of larger mammals, including primates. They demonstrate the relation of the supernormal period to the descending limb of the T wave in rapidly beating hearts when there is no U wave, and to the U wave when it is present.

THE U WAVE IN MAN

The Presence of the U Wave.—Two conditions are essential for detection of the U wave: (1) a sufficiently slow heart rate, and (2) the absence of auricular fibrillation. Since the U wave follows T, and precedes P, the diastolic interval must be long enough to prevent obscuring of the U by the oncoming P. In man the maximum rate which permits recognition of U is between 90 and 100. This is well illustrated by Fig. 3*B*, in which, with sinus arrhythmia and a rate ranging from 105 to 75, the U wave is shown gradually emerging from beneath the P wave. In children, a conspicuous U wave may be seen with considerably higher heart rates (Fig. 3*A*). While U waves can at times be seen when the auricles are fibrillating and the ventricular rate is slow, the irregular auricular waves usually make it difficult, if not impossible, to identify them.

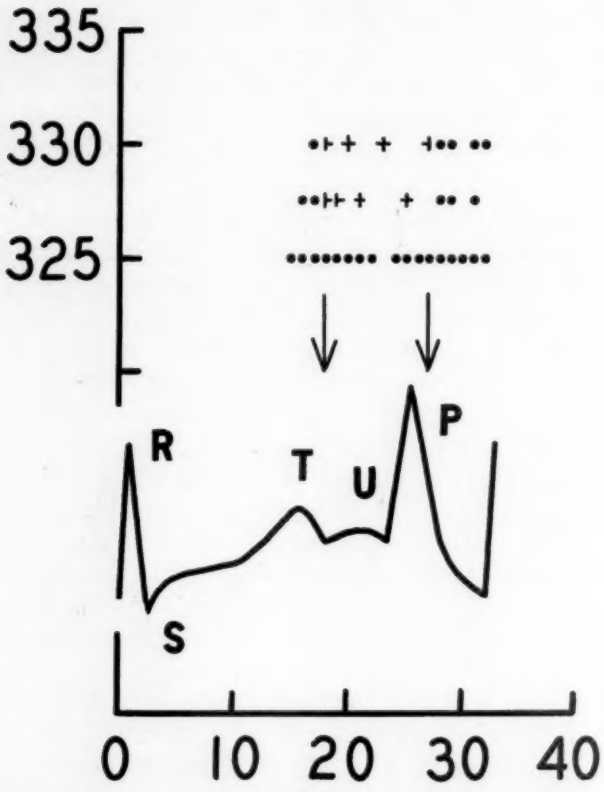

Fig. 2.—Dog, 20 kg. Sodium amytal anesthesia. Chart constructed as in Fig. 1. The arrows indicate the supernormal period, which here falls on the U wave.

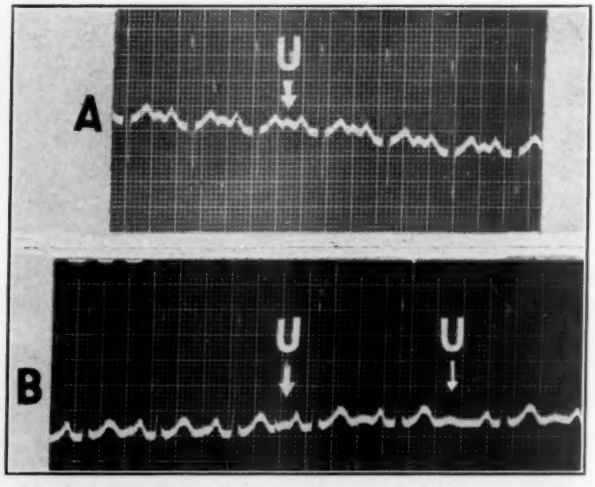

Fig. 3.—*A*, Lead IV R from a 15-year-old boy, showing a U wave, with a heart rate of 150; *B*, Lead IV R showing U wave emerging from beneath P as the heart slows.

Of 151 electrocardiograms without manifest evidence of abnormality, the U wave was recognized distinctly in 10 per cent in Lead I, 10 per cent in Lead II, 6 per cent in Lead III, and 75 per cent in Lead IV R. Only those U waves which had an amplitude of more than 0.25 mm. and a duration which could be measured definitely were recognized. This

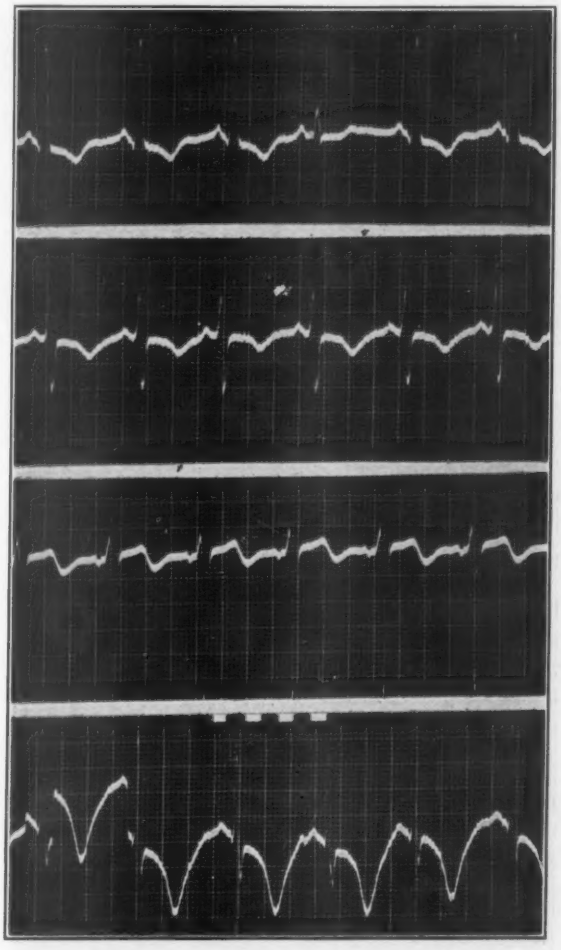

Fig. 4.—Leads I, II, III, and IV R, reading from top to bottom, showing wide T waves in a patient with coronary artery disease.

may account for the lower frequency of U waves in the conventional leads in this series than in that of Lewis and Gilder. It does, however, render all the more striking the higher incidence of U waves in Lead IV R.

By contrast, in the electrocardiograms of ninety-three patients showing evidence of myocardial disease, the incidence of the U wave in Lead IV was only 40 per cent, and 4.4 per cent in Lead I. Lead II, with

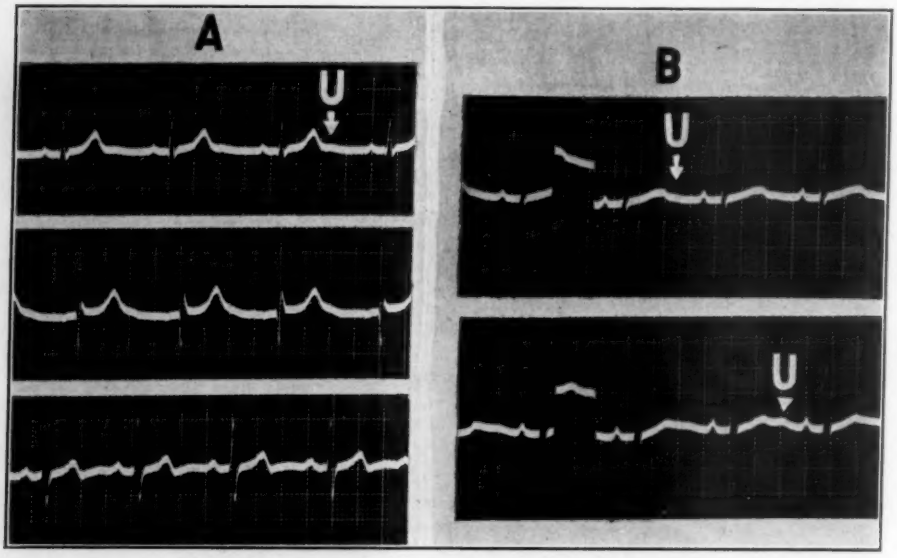

Fig. 5.—*A*, Leads II, III, and IV R, showing U on the terminal portion of T. *B*, Leads II and IV R which also show a confluence of T and U.

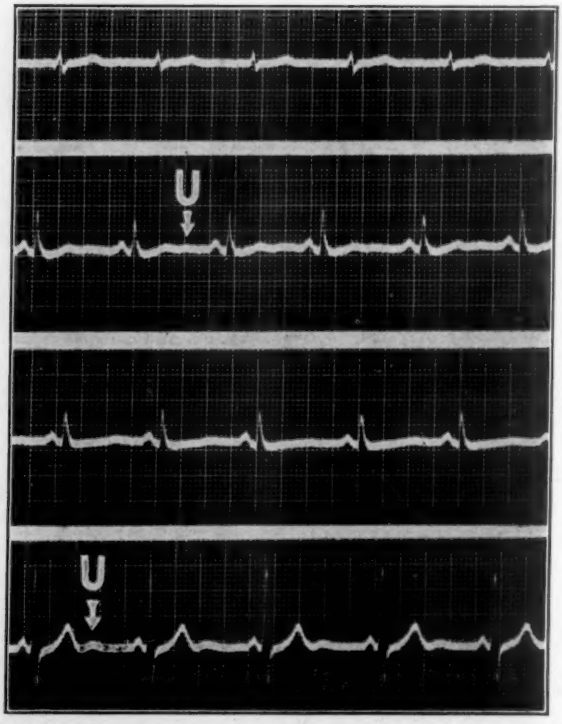

Fig. 6.—Records from Leads I, II, III, and IV R, showing fusion of T and U in Lead III.

10.1 per cent, and Lead III, with 7.4 per cent, were practically the same as normal. At least one reason for this is apparent in some records. Fig. 4 is taken from a patient with hypertensive heart disease and cardiac infarction, and shows a remarkable widening of the S-T interval, extending in Lead IV as far as the onset of P. In such a record a U wave would of course be entirely obscured. An earlier stage in this same process, with incomplete fusion of U and T, is shown in Fig. 5*A*, which is the record of a patient with coronary thrombosis. An even earlier stage is found in Fig. 5*B;* in this case the only diagnosis made by the electrocardiogram was right axis deviation, while the clinical diagnosis was active rheumatic heart disease. Thus far, such a fusion of T and U has been found only in records of patients with damaged hearts. Occasionally in such hearts the fusion may be marked in one lead, and not exist in the others (Fig. 6, Lead III).

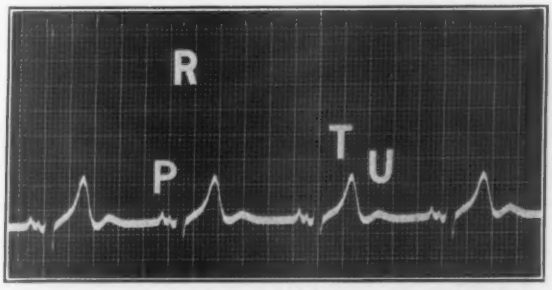

Fig. 7.—The most pronounced U wave found in a normal subject, Lead IV R.

Amplitude and Direction.—The U wave in normal subjects appears as a low summit never more than 1.50 mm. high, but more often from 0.25 to 0.75 mm. It usually begins 0.04 second beyond the end of T, and continues for 0.16 to 0.24 second, with an average duration of 0.20 second (Fig. 7). While in the normal subjects the U wave was invariably upright, this was not the case in the patients with damaged hearts. As mentioned above, only 40 per cent of the patients with damaged hearts showed any kind of a U wave in Lead IV R. Of these, thirty-six in number, twenty-four were found to exhibit an inverted U wave. The inverted U wave was thus found only when heart disease was present, and at times was the only electrocardiographic evidence of damage. Two examples of this are shown in Fig. 8. In *A, B,* and *C* are shown Leads I, II, and IV R from a patient with hypertension, arteriosclerosis, and coronary sclerosis; the inverted U is practically the only electrocardiographic evidence. In D is shown Lead IV R of a patient with hypertensive and coronary heart disease with congestive failure, and again the inverted U is the only abnormal electrocardiographic sign. Fig. 9, *A* and *B,* shows Leads III and IV from a patient with bundle branch block, and shows a negative T and a negative U in

Lead III, but positive T and U in Lead IV R. Inversion of the U wave was not associated with any one specific disease, but with a variety. The most common were coronary artery disease, with or without thrombosis, rheumatic valvular disease, hypertensive heart disease, and pulmonary heart disease.

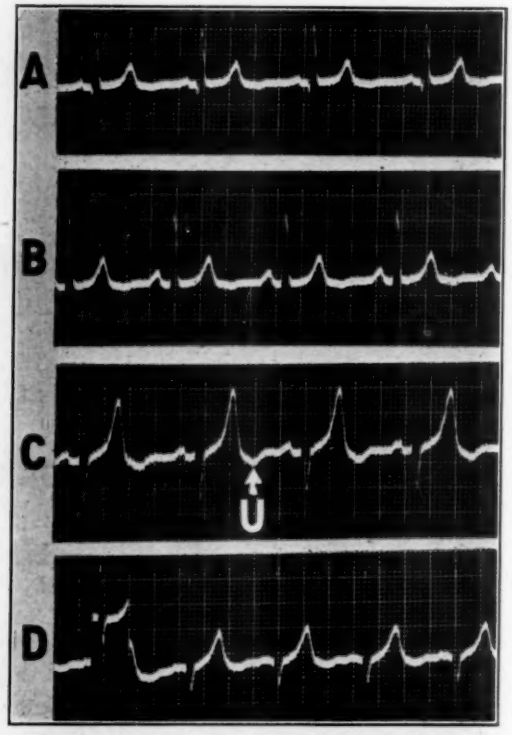

Fig. 8.—*A*, *B*, and *C* are Leads I, II, and IV R from a patient with arteriosclerosis, coronary sclerosis, and hypertension, showing negative U waves with positive T waves. *D* is Lead IV R from another patient with hypertensive heart disease, showing negative U waves.

Certain circumstances alter the amplitude of U. Following ventricular extrasystoles the U wave may become much more pronounced, as in Fig. 9*C*, but may also disappear, as in Fig. 10. The U wave may be pronounced in cases of bundle branch block, as shown in Fig. 9, *A* and *B*, though this is again not invariably so.

The U Wave and Extrasystoles.—In seven of the records included in this study a bigeminal rhythm was found. In all these the ectopic beat fell either on a clearly marked U wave (Fig. 10, *A* and *B*) or in that part of the cycle in which the U wave is found (e.g., within 0.024 second after the termination of T). Study of the position of the ectopic beat in published records of begeminy confirms this completely. It was noted that while an exact coupling was often found, at other times the onset of the premature beat varied within limits of 0.06 to 0.08 second.

Isolated extrasystoles of ventricular origin were found to occupy three parts of the cycle, depending on the rate of the heart (Fig. 11). By far the greatest number, occurring in hearts beating at intervals of 0.60 to 0.80 second, fell either on the U wave (Fig. 10, *A* and *B*) or within 0.24 second after the end of T. With more rapid rates extrasystoles were less frequent, but in one record in which extrasystoles were found they appeared on the descending limb of T (Fig. 10, *C* and

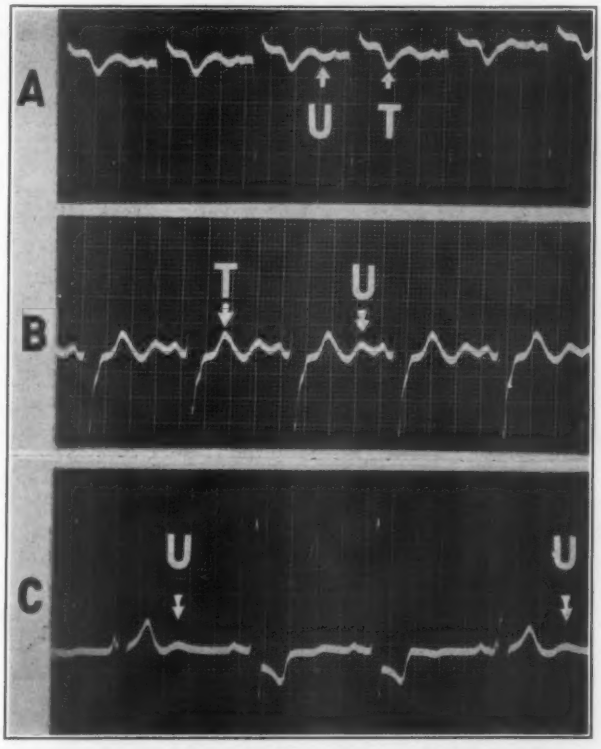

Fig. 9.—*A* and *B* are Leads II and IV R, and show the pronounced U wave in intraventricular block and a negative U. *C* is Lead IV R, showing the pronounced U waves following ventricular extrasystoles.

D). It should be recalled that in cats, dogs, monkeys, and the chimpanzee, rapid rates revealed that the supernormal period lay on the descending slope of T. In slowly beating hearts isolated extrasystoles may fall late in the cycle (Fig. 11), in addition to falling upon the U wave. The slowness of rate and the lateness of the extrasystoles suggest that these may be caused by the well-known phenomenon of ventricular escape. Thus two types of extrasystoles may be discerned, the first of the escape type, not related to the U wave, and the rest, including the coupled extrasystoles in bigeminy, which fall in the part of the cycle occupied by the U wave.

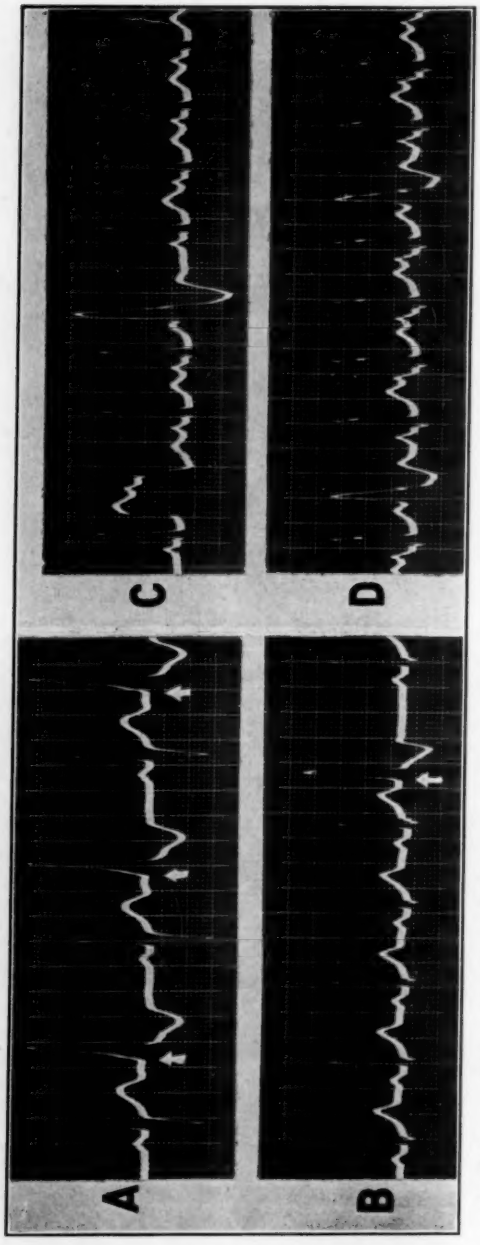

Fig. 10.—*A* and *B* are Lead IV R from two subjects, showing ventricular extrasystoles falling on the U waves. *C* and *D* are Lead IV R from two other subjects, showing ventricular extrasystoles falling on the descending limb of the T wave in hearts beating more rapidly. Compare these with Figs. 1 and 2.

Experimentally, this period is found to be the time of supernormal excitability, when this phenomenon exists. The fact that the majority of ventricular extrasystoles occur at this same time may be more than a mere coincidence, and may indicate the existence of some correlation between the supernormal period and certain extrasystoles.

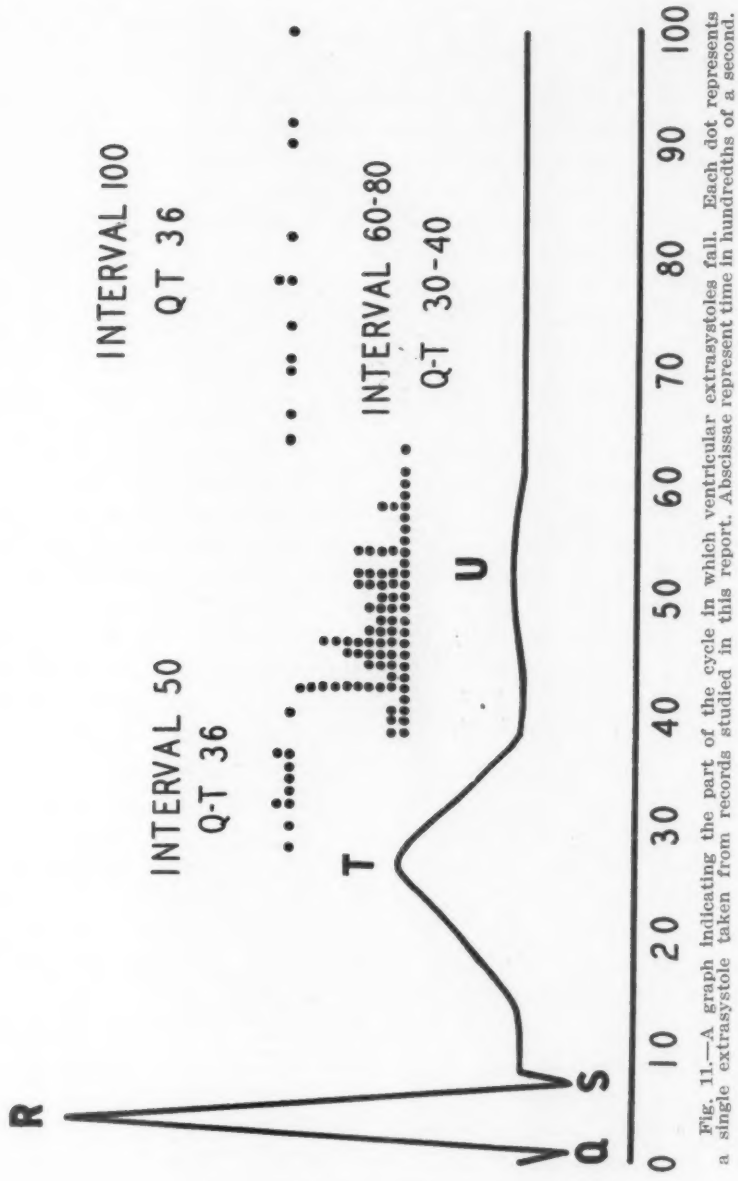

Fig. 11.—A graph indicating the part of the cycle in which ventricular extrasystoles fall. Each dot represents a single extrasystole taken from records studied in this report. Abscissae represent time in hundredths of a second.

DISCUSSION

Experimental evidence furnished elsewhere and confirmed and extended in this report proves that beyond the T wave are to be found electrical events (*the U wave*) associated with the recovery phase of the previous systole, and that the end of the T wave does not mark the end of electrical systole. This period of continuing electrical activity is the U wave, and is the site of the supernormal phase when it is present. The existence of a U wave in the human electrocardiogram in the same

part of the cycle as in other animals indicates that in man also the U wave is a part of the ventricular complex, and marks that part of the cycle where a supernormal phase can be expected.

The basic investigations of Erlanger and Gasser on the recovery cycle in nerve have demonstrated that the supernormal period is associated with the negative after-potential. This after-potential and the supernormal period associated with it have been shown to be particularly variable, and are capable of being increased by acid, asphyxia, and certain drugs such as veratrine, and decreased by factors which improve the metabolic condition. Although the U wave thus represents the negative after-potential, it must be remembered that it is in reality the summation of events in individual fibers, and therefore is influenced by physical factors of position and distribution of muscle mass as well as by factors that change the after-potentials themselves. This is clearly shown by its variation in different leads. This makes it difficult to draw conclusions concerning the supernormal period and the negative after-potentials from the state of the U wave. Nevertheless, since the experimental evidence clearly shows that changes in the metabolic condition of the tissue are reflected in changes in the negative after-potential, it might be expected that the U-wave changes would be found in some damaged hearts. This, in fact, has been noticed in the analysis of records from ninety-three patients with diseased hearts. The U wave tends to disappear from Lead IV R, to fuse with the T wave in all leads, and to become inverted. In fact, neither a negative U wave nor a fusion of T and U was ever observed in electrocardiograms from persons with normal hearts.

The usual concept that the end of T is the end of the electrical cycle is no longer tenable. This is dramatically illustrated in Fig. 12, showing a number of electrocardiograms in which it is difficult to detect in Lead IV R the demarcation between T and U or to assign to any point in diastole the end of the ventricular complex.

Study of the extrasystoles which occurred in this group of records revealed that they fell, with few exceptions, during the part of the cycle in which a supernormal period might be expected to exist. The only exception was that when the heart was beating very slowly they might have been a manifestation of the well-known phenomenon of ventricular escape, and not at all related to a supernormal phase. Previous workers have already suggested a causal relationship between the supernormal phase and extrasystoles. Gasser noticed that nerves showing a marked supernormal phase were likely to respond to a single stimulus by prolonged repetitive discharge, during which each succeeding discharge occurred at the height of the supernormal period following the previous beat. He explained this on the basis of an internal subliminal stimulus which was incapable of initiating spontaneous activity when the tissue was at rest. When, however, the nerve was once stimulated,

the resulting supernormal phase lowered the threshold to a point where the latent internal stimulus became effective. This reasoning was applied to the Purkinje fibers of the heart by Goldenberg and Rothberger.[9] In the heart it is known that the ventricular conduction system possesses an inherent automaticity, usually subliminal. If, however, a marked supernormal phase develops, it is possible that at this time the latent stimulus will become effective, and evoke an extrasystole.

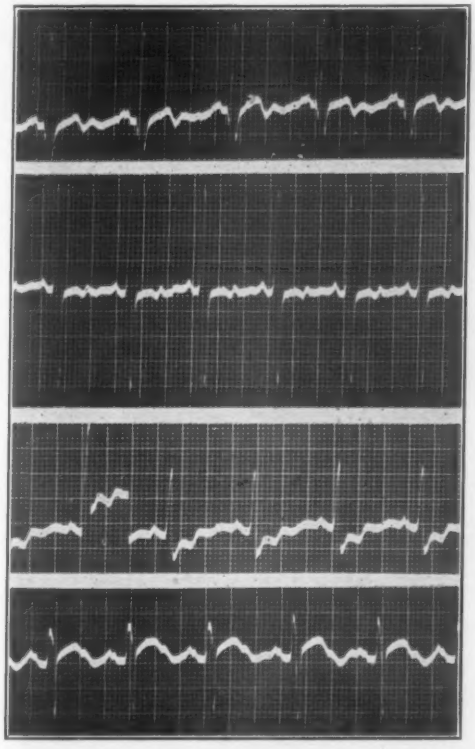

Fig. 12.—Records from Lead IV R which illustrate the difficulty occasionally encountered in determining the end of T and U.

Upon the supernormal period may thus depend the type of arrhythmia which develops. If it is not marked, the latent stimulus may be insufficient to produce a response; if it comes and goes, as it was seen to do in experiments, isolated extrasystoles would be found at various points in the period. If continually present it might produce bigeminy, or even an attack of paroxysmal tachycardia.

It is of course obvious that the intensity of the internal stimulus must play an important part. Whatever the effect of the supernormal phase, if the internal stimulus is inadequate no response may be expected. On the other hand, heightened automaticity of the conduction system may evoke discharge without the help of a supernormal phase. Ventricular

escape from vagal inhibition is an example of this, as are the ventricular rhythms in A-V block and the ventricular beats following intravenous injection of adrenaline.

SUMMARY

1. The U wave of the human electrocardiogram is a part of the ventricular complex.

2. It represents the part of the cycle in which the supernormal phase occurs.

3. It tends to disappear in some cases of heart disease.

4. Inversion of the U wave or fusion of the U wave with the T wave is found only in patients with damaged hearts.

5. The majority of ventricular extrasystoles fall on the U wave or the part of the cycle where it occurs.

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A NEW ELECTRODE FOR RECORDING BIOELECTRIC POTENTIALS

HOWARD L. ANDREWS, PH.D.*
LEXINGTON, KY.

THE electrodes described here were developed for use in the recording of electric potentials of cortical origin under conditions where eases of application and removal were of paramount importance. They were designed originally for use in a study of cortical potentials during the withdrawal phase of drug addiction, when the patient is highly irritable and objects to the use of collodion-cemented electrodes so commonly used in electroencephalography. These electrodes have proved so valuable for general use in electroencephalography and electrocardiography that a detailed description seems warranted.

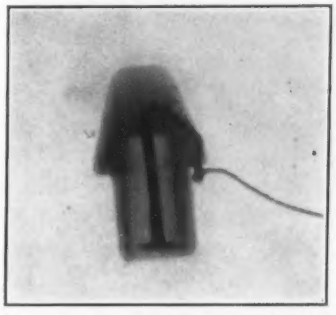

Fig. 1.—Roentgenogram of a completed electrode.

A disk 5 mm. in diameter with a thin tail 5 cm. long is cut from sheet silver about 0.5 mm. thick. The tail is bent up at right angles to the disk. The tail is then forced through the top of a rubber eraser of the type which slips over the end of an ordinary lead pencil. The tail is bent over and forced through the edge of the rubber at its thickest point. This prevents bending of the silver at the point where it emerges from the rubber. This point is sealed with wax to make a leak-proof joint. The lead wire is soldered to the silver near the point where the latter passes through the rubber rim. Fig. 1 shows a roentgenogram of a finished electrode. There are undoubtedly other rubber products available which would be suitable for making these suction cups. The erasers have been used because of their convenient size (contact area about 1 cm. in diameter), their availability, and low cost.

If these are applied to the scalp surface it is necessary to cut the hair over an area large enough to accommodate the end of the rubber cup. A

*Associate Physicist, United States Public Health Service, from the United States Public Health Service Hospital, Lexington, Ky.
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small amount of electrode jelly is placed in the cup and around the end. When squeezed to expel the air, pressed firmly against the skin and released, the cup will hold securely for at least an hour. When properly applied, these cups will withstand a surprising amount of pull and movement of the patient.

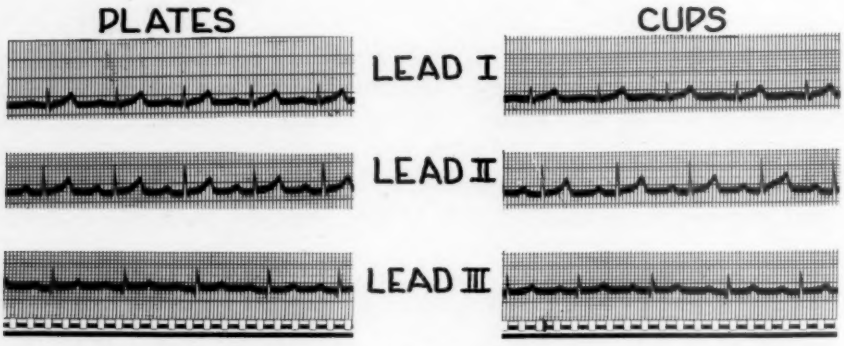

Fig. 2.—Comparison of plate and cup electrodes. In Lead I there is a low background of muscle potentials, but this is the only difference between the records.

If a nonpolarizable electrode is desired, a solution of 0.1 normal hydrochloric acid is quite satisfactory. Some of the solution is drawn up inside the cup and the latter arranged so that the end just dips into the solution. The cups are connected to the positive pole of a dry cell. A small piece of silver serves as the cathode. A satisfactory coat of silver chloride is obtained in three or four hours. If chlorided electrodes are used they should be kept moist when not in use to preserve the chloride coating. This is easily accomplished by using a short piece of rubber tubing just large enough to slip over the end of the rubber eraser. An excess of electrode jelly is placed in each suction cup and the latter is slipped into the tubing. If one cup is put in either end of the tubing air is excluded and the electrodes will be kept in good condition.

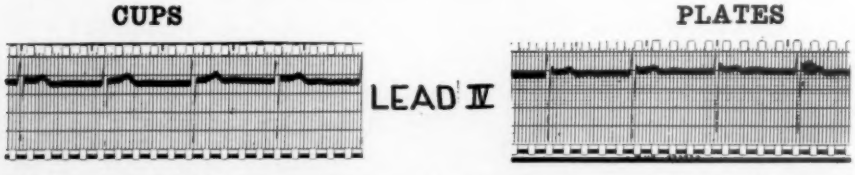

Fig. 3.—Comparison of Lead IV records taken with plates and cups. In the record taken with plates there is an overswing when the S-wave returns to the axis. This may be due either to electrode polarization or to the lack of precise localization of the apical point with the large electrodes.

Simultaneous electroencephalograms taken with a pair of collodion cemented electrodes and a pair of suction cups placed close to the cemented electrodes (but not in contact) showed no significant differences.

When used for electrocardiographic electrodes the disks can be made of zinc and no chloriding is necessary. In this application even a heavy growth of body hair does not interfere with the vacuum, so that no hair cutting is necessary.

Fig. 2 shows a series of consecutive electrocardiograms taken first with the regular plate electrodes and then with the suction cup electrodes. There are no important differences between the two sets of records.

In some cases there is a low amplitude background of muscle potentials in the suction cup records, but in no case is this objectionable, and in many cases it is absent. It can usually be removed by a slight change of the position of the cup.

The suction cup is particularly suited for the precordial contact in Lead IV. The desirability of keeping this electrode small has been emphasized in the report of the committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland.[1, 2]

When the region around the position of the apex beat is explored with one of the cup electrodes it is found that the records obtained show large variations from the records taken directly over the apex beat. Any large electrode will record an integrated effect which will differ from the true record obtained with the smaller electrode. Fig. 3 shows a comparison of Lead IV records taken with the small suction cup and with a plate 3 cm. in diameter. In this case the suction cup was nonpolarizable, and it is believed that the record from this electrode is a more accurate representation of the electrical activity existing at the apex.

If the electrocardiograms are recorded with a string galvanometer, with no intervening amplifier, the resistance of the small cups may cause trouble. The resistance between the pair of 1 cm. cups described is about 8,000 ohms. This is not high enough to cause trouble if they are connected to a vacuum tube amplifier. In cases in which electrode resistance was important, larger cups, 3 cm. in diameter, have been successfully used. A pair of these cups shows a resistance of about 1,500 ohms. Cups of the type used to fasten appliances to automobile windshields have a diameter of about 3 cm. and are quite satisfactory if low resistance contacts must be obtained.

I take this opportunity to express my appreciation to Dr. C. K. Himmelsbach for helpful suggestions and for critically reading the manuscript.

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ENLARGEMENT OF THE HEART IN INFANTS AND YOUNG CHILDREN

M. A. KUGEL, M.D.
MIAMI BEACH, FLA.

CONGENITAL "idiopathic hypertrophy" of the heart is a term long used to designate cardiac enlargement with no apparent cause; upon pathologic investigation, only hypertrophy of the heart muscle is found. To anyone who has had experience at the autopsy table, the term "idiopathic hypertrophy," applied to great enlargement of the heart, seems very inappropriate. An organ does not enlarge beyond normal limits unless there is some underlying pathologic-physiologic disturbance, even though we may be unable to recognize it with our limited knowledge of today.

In a review of the literature[1] there was collected a series of cases of cardiac enlargement which were reported as instances of congenital idiopathic hypertrophy. A study of these cases, even as reported, revealed that most of them were not genuine examples of congenital idiopathic hypertrophy of the heart, since either myocardial disease or other factors were found in the post-mortem examination which could have had a causal relationship to the cardiac enlargement.[2, 3]

In 1933, Kugel and Stoloff[1] described seven cases of unusual enlargement of the heart in infants and young children which hitherto might have been regarded as examples of idiopathic hypertrophy. In all instances the clinical picture and the pathologic changes in the myocardium were similar. Later, further investigation of fresh pathologic material with chemical examinations in another similar case confirmed the original impression that this form of cardiomegaly was different from von Gierke's disease and other types of cardiac enlargement (Table I).

TABLE I

CAUSES OF ENLARGEMENT OF THE HEART IN INFANTS AND YOUNG CHILDREN

I. *Congenital Defects*
- a. Heart
- b. Coronary arteries
- c. Aorta and pulmonary artery

II. *Infections*

a. Unknown etiology	Rheumatic fever Fiedler's myocarditis Periarteritis nodosa, etc.
b. Known etiology	Diphtheria Scarlet fever, etc. Subacute bacterial endocarditis, valvular defect Syphilis, etc.

Dedicated to the late Dr. Louis Gross, brilliant investigator in the field of cardiovascular disease, teacher, collaborator, and friend.

Received for publication Nov. 1, 1938.

III. *Anemias (of long standing)*
- a. Primary anemia
- b. Secondary anemia

IV. *Syndrome of nonsuppurative "myocardial degeneration with dilatation and hypertrophy"*

V. *Metabolic*
- a. Avitaminosis—beriberi, etc.
- b. Thyroid deficiency
- c. Glycogen-storage disease, von Gierke

VI. *Hypertension*
- a. Greater circulation { Essential; Adrenal tumors; Secondary to kidney lesions (inflammatory or congenital) }
- b. Lesser circulation (lesions in lung, kyphoscoliosis, etc.)

VII. *Tumors of Heart*
- a. Primary
- b. Secondary

VIII. *Unclassified Group*

CASE REPORT

G. H., Case No. 8, an 8-month-old colored girl who had previously been well, was admitted Nov. 22, 1934, to the Mount Sinai Hospital on the service of Dr. Bela Schick with a history of a cough for one week previous to admission. The cough had become worse in the preceding two days, and had occurred in paroxysms, often lasting an hour or more. At no time did the child appear acutely ill. When she was examined by the family doctor there was only a slight fever and the throat was slightly red. The doctor stated that the "chest was clear." Argyrol was applied locally to the nose.

The mother, 25 years of age, was living and well; she had had one miscarriage, which occurred at the third month of gestation. There were no other children. There was no apparent history of tuberculosis, syphilis, or other diseases. Both parents were colored.

The child was born in New York City, at full term. The delivery was normal. The baby weighed 7 pounds and showed no evidence of cyanosis or icterus. It breathed and nursed normally and was breast-fed until it was 5 months old. The diet was then supplemented by cow's milk. Orange juice had been given since the child was 3 months old, and cod-liver oil (a teaspoonful three times a day) for the preceding four to five months. It gained normally. The child had had occasional colds.

On examination the child appeared to be acutely ill. She had an almost continuous high-pitched cough. There were dyspnea and cyanosis. The temperature was 97.6° F.; the respiration rate 44. There were many vesicular lesions, some of which were pustular, over the anterior part of the thorax, the neck, and forehead. There were enlarged lymph nodes at both angles of the jaw, and in the posterior cervical, inguinal, and epitrochlear regions. There was an area of dullness extending over the left anterior chest to the axilla. Many crepitant and subcrepitant râles were heard, most marked on the left side. The heart rate was 160 and the rhythm was normal. The heart sounds were poor in quality. The blood pressure was 72 systolic. The abdomen was protuberant. The spleen was soft, extending one fingerbreadth below the costal margin. The liver was two fingerbreadths below the costal margin.

Roentgenologic examination of the chest showed a very marked enlargement of the heart to the left, extending out to the axilla; on the right side it extended to the midclavicular line. The enlargement also involved the entire base (Fig. 1).

A certain amount of magnification and distortion of the heart shadow was due to the fact that the examination could be made only in the anteroposterior position; the usual standard method could not be used.

An electrocardiogram taken Nov. 23, 1934, showed sinus tachycardia with a rate of about 150 beats per minute, low amplitude of QRS in Lead I, and T waves of low amplitude (Fig. 2).

On Nov. 23, 1934, the child was seen in consultation by the author and a diagnosis of primary myocardial degeneration with dilatation and hypertrophy of the heart was ventured because of lack of the usual signs of congenital cardiac defects, as well as of evidence of diseases such as rheumatic fever, diphtheria or beriberi.

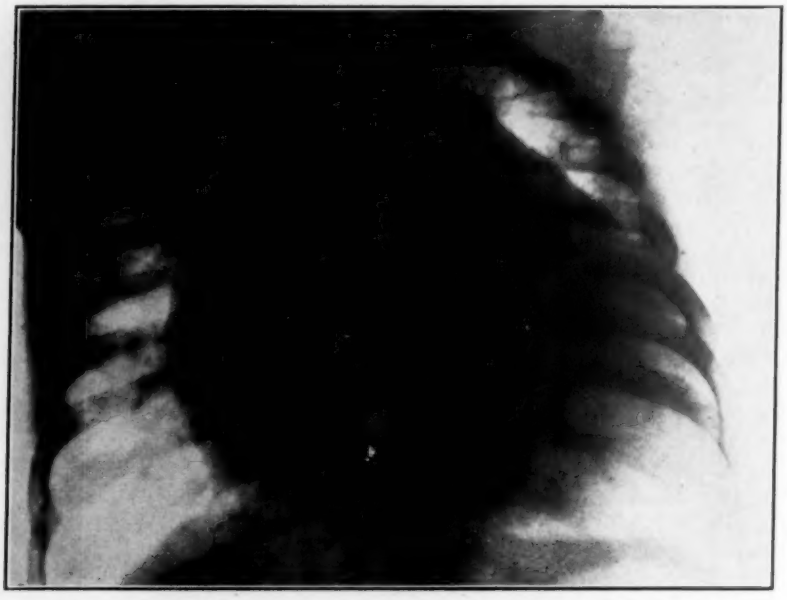


Fig. 1.—Case 8. Roentgenogram of chest showing marked enlargement of heart with dilatation of left ventricle and some prominence of right border.

The sugar content of the blood was 65 mg. per cent, the urea 11 mg. per cent, the cholesterol 235 mg. per cent, and the cholesterol ester 75 mg. per cent. The blood Wassermann reaction was positive (4 plus) on two occasions. The blood Kahn test was negative. The urine was normal. The hemoglobin was 60 per cent, the erythrocyte count 3,640,000, and the leucocyte count 32,000; the differential leucocyte count showed 46 per cent polymorphonuclear leucocytes, of which 2 per cent were myelocytes and 1 per cent eosinophiles. Examination of the blood smear revealed some hypochromia and toxic granules in a few of the polymorphonuclear leucocytes.

The child showed no signs of improvement throughout her stay in the hospital and died of myocardial failure on Nov. 25, 1934.

The clinical diagnosis was (1) enlargement of the heart (so-called "congenital hypertrophy"), (2) rickets, and (3) miliaria.

Post-mortem examination was performed under the direction of Dr. Paul Klemperer. The findings were as follows: The body of the poorly developed and undernourished 8-month-old female colored child showed no evidence of jaundice or edema. The abdomen was distended, with a slight bulge at the umbilicus. The liver's edge reached down to the level of the umbilicus and the liver occupied the

entire upper abdomen, displacing the spleen posteriorly. The spleen was also enlarged, extending to the level of the umbilicus. The heart was markedly enlarged. The left ventricle extended almost to the left lateral thoracic wall, displacing and compressing the left lung laterally and posteriorly. The right border, formed by the bulging right auricle and enlarged right ventricle, was in the region of the right midclavicular line.

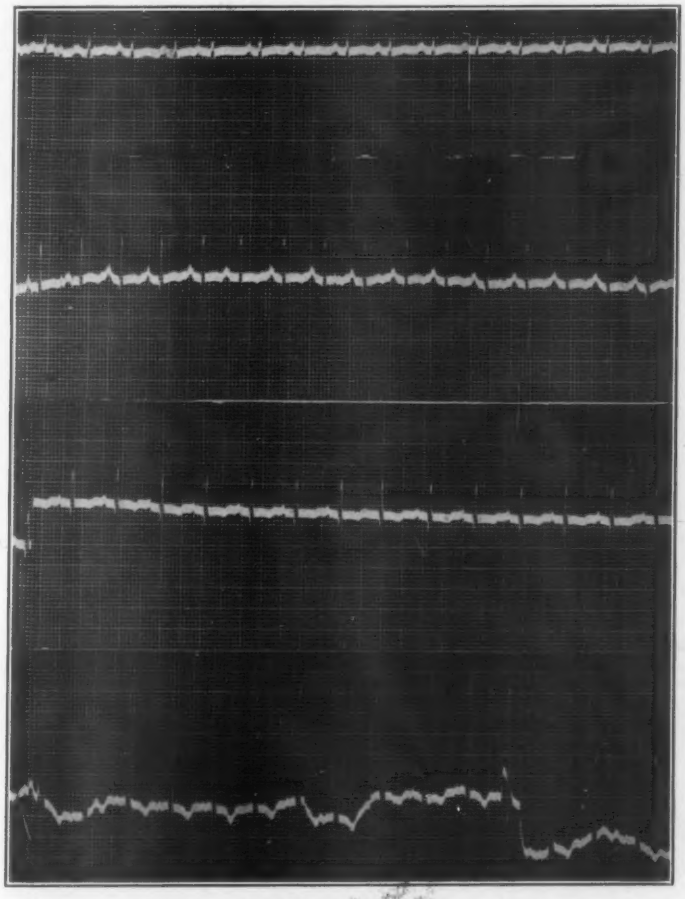


Fig. 2.—Case 8. Electrocardiogram showing sinus tachycardia, QRS of low amplitude, in Lead I, and T waves of low amplitude, indicating myocardial involvement.

The heart weighed 90 gm. (Fig. 3). On the anterior aspect of the pericardial sac there was a diffuse hemorrhagic area (ante-mortem pericardial puncture). The pericardial sac contained a small amount of clear straw-colored fluid and was otherwise entirely occupied by the enlarged heart. The coronary veins were congested and prominent beneath the visceral pericardium. The epicardial surface of the upper posterior portion of the left ventricle was discolored, presenting a dark, reddish, mottled aspect over an area 3 by 4 cm. in size. The right auricle was markedly dilated and its wall slightly hypertrophied. The right ventricle was also markedly dilated and somewhat hypertrophied. The trabeculae carneae were prominent. The myocardium of the right ventricle measured 4 mm. in thickness at its midportion, and 3 mm. at the apex. The left ventricle was markedly dilated. Its walls were hypertrophied. The myocardium of the left ventricle measured 7 mm. in thickness

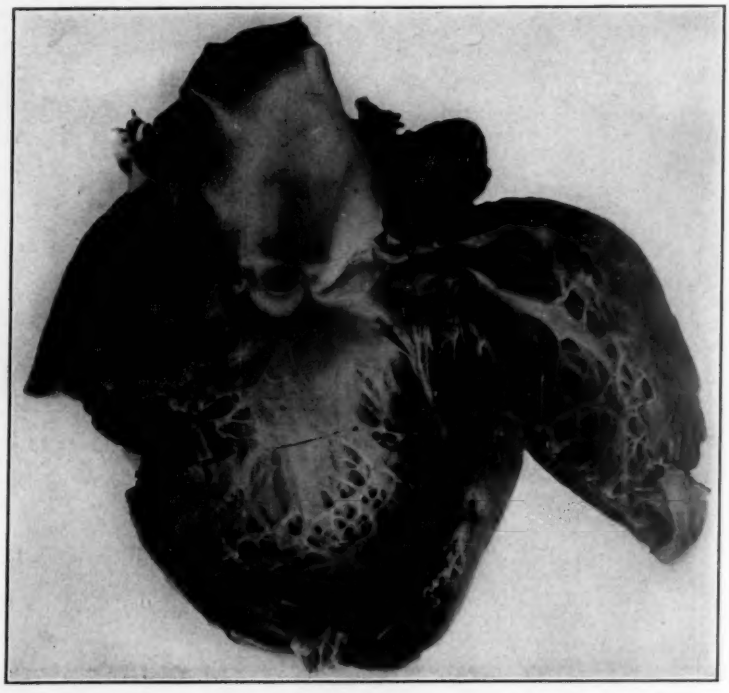
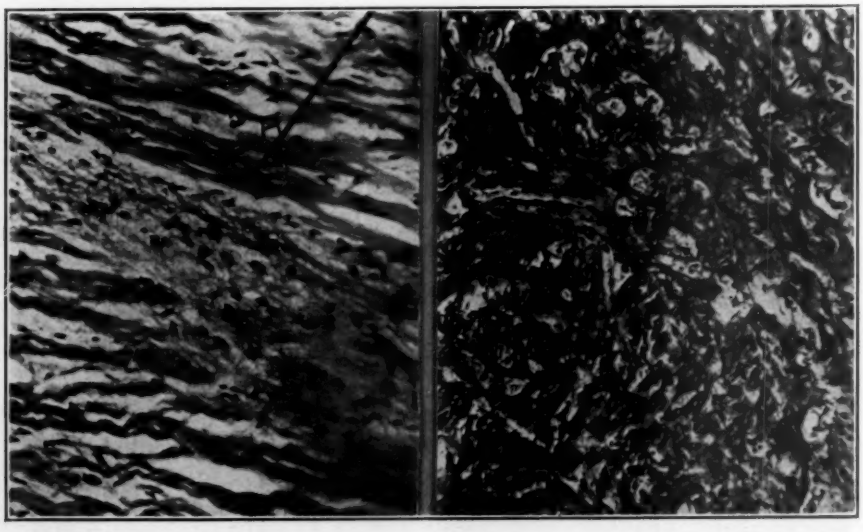


Fig. 3.—Case 8. Photograph of enlarged heart showing dilatation and hypertrophy of the left ventricle and appearance of myocardium.



A. *B.*

Fig. 4.—Case 8. Photomicrographs of ventricular musculature of heart showing (*A*, see arrow) focus of myocardial degeneration and (*B*) distortion of muscle fibers.

at its midsection and 5 mm. at the apex. The outflow tract of the left ventricle measured 4.8 cm. in diameter. The myocardium, on section, was dull, pale, and grayish-brown throughout. The endocardium of the left ventricle was thickened and whitened. The valves presented no gross changes. The foramen ovale was small. The coronary ostia were patent and normal in origin and distribution. The ductus arteriosus was obliterated. The aorta showed no abnormalities. The lungs were the seat of a bronchopneumonia.

The liver, light yellow-brown in color, was large, and its surface was smooth and glistening. The spleen was large and firm. The kidneys were slightly enlarged. The thymus was not enlarged. The bone marrow was cellular, red in color, and had normal bone trabeculae. The costochondral junction presented a distinct narrow line. The osteochondral boundary at the head of the humerus (left) was also fine and distinct. The periosteum of the upper humerus (left) showed no gross changes.

Microscopic Examination.—The lung sections showed bronchopneumonia. The myocardium showed focal areas of degeneration (Fig. 4). In the vicinity of the fibrous areas in the myocardium there were occasional muscle fibers with vacuoles. Some of the muscle fibers showed atrophy and degeneration with replacement fibrosis. There were no areas of suppurative cellular infiltration. The blood vessels showed no marked changes. A few lymphocytes were found in the pericardium. The endocardium was thickened.

The liver contained a small amount of fat. The kidneys were negative, as also were the adrenals, pancreas, spleen, and lymph nodes. The skeletal muscle was negative.

Glycogen stains showed only a moderate amount of glycogen, uniformly and normally distributed, in the heart, lungs, liver, kidneys, and skeletal muscle. There was no clinical, pathologic, or chemical evidence of von Gierke's disease. Sudan stains revealed only a small amount of fat. The Levaditi stains for spirochetes in the heart and kidneys were negative, and a thorough gross and microscopic examination failed to reveal evidence of congenital syphilis.

Post-Mortem Diagnosis.—Cardiac dilatation (marked), all chambers; cardiac hypertrophy (moderate); acute congestion of liver, spleen, kidneys; fatty changes in liver; partial atelectasis of lungs, including all lobes; bronchopneumonia.

This case, No. 8, just described in detail, proved to be very important. The clinical picture and pathologic lesions were similar to those in our seven cases previously reported.[1] In the eighth case, however, we were able to make chemical, as well as microscopic, studies of fresh heart muscle, skeletal muscle, and other organs, and definitely ruled out abnormal glycogen-storage disease. A study of this group of eight cases has enabled us to recognize this form of cardiomegaly clinically.

SUMMARY OF THE CLINICAL AND PATHOLOGIC FINDINGS IN THE SYNDROME OF NONSUPPURATIVE MYOCARDIAL DEGENERATION WITH DILATATION AND HYPERTROPHY

Definition.—A well-defined syndrome in infants and young children characterized clinically by an unusual degree of enlargement of the heart, electrocardiographic abnormalities, an afebrile course, a tendency to abrupt onset of myocardial failure, and the suddenness with which death may occur.

Etiology.—The etiology of this disease is at present undetermined. Many theories have been advanced but none proved.[1] In most of the cases the disease has been recognized before the second year of life (Table II).

TABLE II

SUMMARY OF EIGHT CASES OF CARDIAC ENLARGEMENT ASSOCIATED WITH NONSUPPURATIVE MYOCARDIAL DEGENERATION

CASES	1	2	3	4	5	6	7	8
Age	8 mo.	6 mo.	3 mo.	15 mo.	4 mo.	3 mo.	6½ yr.	8 mo.
Sex	M	M	F	M	M	M	F	F
Symptoms								
Dyspnea		x	xxx		x	xxx	xxx	
Cyanosis		x	xxx	x	x		x	x
Vomiting	xxx	xxx		xxx			xx	
Cough				x				xxx
Total known duration of illness	6 wk.	1 day	4 days	2 wk.	5 days	1 day	10 wk.	6 days
Heart Weight in Grams								
Normal (average)	33	32	22	45	22	22	84	33
*Actual	75	90	Marked enlargement	155	85	75	190	90

*Percentage increase of actual heart weight compared to normal standards was from 120 to 290 per cent.

The disease is apparently not limited to any sex or race. We have observed two cases in adults in which the lesions were similar. Some of those reported by Levy[4] may belong to this group.

The changes in the heart may represent an allergic response to infection, probably due to a virus. Whether this is a specific reaction to a specific infection, or an allergic response to various types of infections, is at present undetermined. The possible factor of infection is the only consistent one we have had.[1] It has also been suggested that these lesions may represent an allergic reaction to milk in a heart which was already damaged by infection.[5]

Symptoms.—The early symptoms of this disease are as yet not too well defined. The respiration may be rapid without any apparent intrathoracic cause. The dyspnea and cyanosis, however, are usually of sudden onset. Fever is generally absent, and the temperature remains normal unless there are complicating independent infections. The heart rate is usually rapid, and the heart sounds are of poor quality. At times a soft, blowing, systolic murmur may be heard at the apex. The cardiac enlargement may not be discovered by physical examination, but roentgenograms of the chest will reveal, usually, a surprising degree of enlargement of the heart.

In the terminal stages of this disease the liver is enlarged. Râles may be heard in the chest, and at times edema occurs. The most striking fact about this entire clinical picture is that the infants or children are usually apparently well and then suddenly develop myocardial

failure, cry, vomit, or refuse food. Unless the chest is examined carefully, the true nature of this condition may not be appreciated.

Roentgenologic examination shows enlargement of the heart to the left and somewhat to the right (Fig. 1). It may be so marked as to fill almost completely the left side of the chest in its transverse diameter. The value of the roentgenologic examination in cases of unexplained dyspnea and cyanosis becomes apparent, since it may reveal a pronounced enlargement of the heart, frequently in the absence of suggestive physical signs. Although the roentgenographic appearance is strikingly suggestive, it is by no means pathognomonic. A similar shadow may be cast in dilatation and hypertrophy of the heart in cases of valvular disease, congenital anomalies, or marked anemia. However, the enlargement of the left auricle and the rumbling murmurs of mitral stenosis, found in rheumatic cardiovalvular disease, are lacking.

Two patients were examined by means of the electrocardiograph and both showed evidence of myocardial damage, such as low voltage, shallow T waves, or prolongation of the P-R interval.

Course and Prognosis.—In five of our cases the patient died on the day of admission. The total duration of illness was usually short (Table II). In two cases it was one day, in one case four days, in another five days, in another six days, in one case two weeks, in another six weeks, and in another ten weeks. Apparently the duration of the disease bears some relationship to the age of the patient. It seems that the older the patient, the longer the disease lasts.

Morbid Anatomy.—The lesions were similar in all of the eight cases. The hearts were dilated and hypertrophied and the weight greatly increased. The endocardium of the left auricle and left ventricle may be thickened. At times bland thrombi may be found attached to the ventricular endocardium in the interstices between the trabeculae carneae. There are no valvular or congenital defects.

On cutting the myocardium, one can see grossly, in some instances, grayish streaks which on microscopic examination prove to be foci of atrophied and degenerated muscle fibers. Atrophy of the muscle fibers with fatty infiltration, muscle degeneration, and replacement fibrosis are the characteristic lesions in all cases. Occasionally a few lymphocytes are found. There are no suppurative foci. The heart muscle arrangement may be so distorted and scarred that it is difficult to recognize (Fig. 4*B*). The coronary arteries showed variable changes, from perivascular fibrosis to hypertrophy of the media and proliferation and desquamation of the intima which at times is sufficient to obliterate the lumen. The valves were in all instances normal. In one instance we found embolic glomerular lesions which could be traced to bland thrombi on the ventricular endocardium.

In our eighth case we found small isolated foci of degenerated heart muscle surrounded by apparently normal myocardium (Fig. 4*A*). This represents probably the earliest lesion of this disease. Even in these

foci there were only a few pyknotic nuclei and wandering cells. Glycogen stains of the myocardium, lungs, liver, and kidneys showed either a small amount, which is normal, or none at all. Sudan stains showed very little fat, while the Levaditi stains showed nothing.

Treatment.—At present little can be said concerning treatment. All of our eight patients died, six within less than a week after admission. Our observations in Case 7 and in two cases in adults, in which symptoms of myocardial failure lasted from ten weeks to three years, give some hope for prognosis and therapy. Prolonged rest, instituted early, and the administration of proper doses of digitalis may have helped in some of these cases. Our only hope in therapy is in the early recognition and the appreciation of the clinical significance of the various types of cardiac enlargement in children.

Diagnosis.—A presumptive diagnosis of the syndrome of cardiac enlargement associated with nonsuppurative myocardial degeneration and fibrosis can be made during life. After clinical and pathologic studies of our first few cases, we were able to predict the presence of this peculiar malady in five instances, in all of which the diagnosis was confirmed at autopsy.

The chief features of this condition are enlargement of the heart without known cause, an afebrile course, the sudden onset of symptoms, dyspnea and cyanosis, and the lack of signs or history suggestive of congenital heart disease, rheumatic fever, diphtheria, infections, anemia, or metabolic disturbances.

DIFFERENTIAL DIAGNOSIS

Congenital Heart Disease.—The finding of an enlarged heart in an infant or a child brings up the problem of differential diagnosis (Table I). Cardiac enlargement in the first few years of life is not infrequently due to a congenital malformation of the heart.[6-9] Congenital heart disease, as outlined in the classical monograph of Abbott,[6] is divided into three clinical groups: (1) the *acyanotic* group, with no abnormal communications between the various chambers of the heart, (2) the *cyanose tardive* group, with an arteriovenous shunt in the circulation and a terminal reversal of blood flow, and (3) the *cyanotic* group, with a permanent venous-arterial shunt and a retardation of blood flow.

Symptoms usually present themselves early in children with congenital heart disease who belong to the cyanotic group. The murmurs heard in this type of congenital cardiac disease are usually loud and rumbling. Roentgenologic examination of the heart may reveal that its outline is bizarre. The contour of the right ventricle, right auricle, pulmonary artery, or aortic conus may be distorted. The electrocardiogram may show right ventricular predominance or other evidences confirming the diagnosis of congenital heart disease.

In the syndrome of cardiac enlargement described, the symptoms usually occur in a child who apparently has been well. Cyanosis in

this instance is only terminal and then not marked. The heart sounds are muffled and at times one hears a soft, blowing murmur at the apex. Roentgenologic examination shows enlargement chiefly of the left ventricle. The left auricle, pulmonary conus, and aortic conus are normal.

It is in the acyanotic group where one finds cases of cardiac enlargement in which the clinical picture is similar to that described by the author. Congenital anomalies of the coronary arteries, such as malposition or maldevelopment, which cause myocardial degeneration, may be followed by marked enlargement of the heart. Such cases have been reported, but are extremely rare.[8, 9]

Abrikosoff[8] was the first to describe a case of this nature. In his case the origin of the right coronary artery was normal, but the left coronary artery originated from the pulmonary artery instead of the aorta. At autopsy there was a marked enlargement of the heart, with an aneurysmal dilatation of the left ventricle. The wall of the left ventricle near the apex was very thin and transparent and was replaced by fibrous tissue.

Bland, White, and Garland[8] have encountered only eight cases in which one of the main coronary arteries, usually the left, arose from the pulmonary artery. In addition, they also report a case of unusual enlargement of the heart associated with congenital anomalies of the coronary arteries.

The clinical diagnosis was "congenital idiopathic hypertrophy" of the heart. Necropsy studies, however, revealed the true nature of the disease. The heart weighed 91 gm. The left ventricle was enlarged and its endocardium showed marked fibrous thickening with occasional patches of fibrosis in the deeper layers. In this case the left coronary artery had its abnormal origin from the pulmonary artery. Had a complete investigation, including post-mortem examination, not been made, this case might have been reported as one of "congenital idiopathic hypertrophy," and this unfortunate term perpetuated in the literature.

In this group we are dealing with a nonsuppurative myocardial degeneration with replacement fibrosis, and the cause of the myocardial damage can be traced to abnormalities in the coronary arteries. In the syndrome described, the cause of the myocardial degeneration is still undetermined. In both instances, however, we have the same pathologic physiology, and therefore it is not surprising that we have the same clinical picture.

Rheumatic Fever.—Enlargement of the heart because of rheumatic infection may be found early in childhood. Rheumatic heart disease occurs in infants and young children more frequently than is generally appreciated. Taran,[10] in a study of 222 children between the ages of 1 and 15 years, found that the highest incidence of rheumatic infection in childhood occurs during school age, that is, from 6 to 15 years. He also found forty cases in infants less than 1 year of age reported in the

literature. Coronary thrombosis of rheumatic origin has been reported in an infant 17 months old.[11]

Poynton[12] found cases of rheumatic heart disease early in life. In a review of 100 patients with acute rheumatism admitted to his ward at the Hospital for Sick Children, he found that thirteen had had the first attack between the ages of 2 and 5 years. Poynton also reports observations on a child of 10 months who had chorea and "acute dilatation" of the heart.

The diagnosis of rheumatic fever in infants and young children can be made if one keeps in mind the fact that this disease can strike early in infancy in the most bizarre fashion. A familial history of rheumatic fever should arouse the suspicion of the presence of this disease in a child with cardiac enlargement.[13-15] The other signs and symptoms to be looked for are: fleeting pains in the joints or muscles; spasmodic twitchings (choreiform movements); and abdominal manifestations, such as cramps or, at times, symptoms simulating intra-abdominal inflammation. Evidence of tonsillitis, pharyngitis, polyarthritis, pancarditis, and myocarditis may be found. Also, there may be continued fever, leucocytosis, abnormal sedimentation time, electrocardiographic changes, etc., which help to establish the diagnosis. When there is a marked enlargement of the heart there is usually a history of rheumatic manifestations. The murmurs are loud and rumbling. Roentgenologic examination may show typical mitralization of the heart, with an enlarged left auricle. The lesions in the myocardium in a case of rheumatic fever are so well known that they need not be described here.

Fiedler's Myocarditis.—Scott and Saphir,[16] in 1929, reviewed thirty cases from the literature. Only two were in children 10 years of age, or younger. One child was 3 years old, and the other was 6. In both cases the heart was enlarged. This disease is extremely rare in infants and young children. Excellent monographs with complete bibliography are available.[16-18] These individuals may have a low-grade fever, signs of myocardial failure, and definite electrocardiographic changes. The heart is the seat of an acute isolated myocarditis and the lesions are characteristic.

Infections of Known Etiology.—The heart may be enlarged when affected by diphtheria, scarlet fever, bacterial endocarditis, syphilis,[19] and other bacterial infections.[20, 21] The problem of differential diagnosis here is a question of the recognition, or the ruling out, of infections of known bacterial origin. The question of other rare forms of myocarditis[21] comes up only when the history indicates such a possibility.

Anemia.—Enlargement of the heart in infants and young children can occur in severe anemia.[22] While in Puerto Rico, visiting Bailey K. Ashford, the author was shown children suffering from hookworm infestation, complicated by severe anemia. The hearts of these malnourished children were apt to be enlarged, and apical systolic murmurs were heard. It was Dr. Ashford's observation that the heart returned to

normal size and the murmurs disappeared when the hemoglobin returned to normal (after the hookworm disease was alleviated or the malnutrition corrected). Similar observations have been reported in adults.[25]

Beriberi.—Vitamin deficiency may lead to beriberi with enlargement of the heart. This may occur in cases of malnutrition and should be suspected particularly in those children who are deprived of proper foods and have enlargement of the heart with symptoms of myocardial failure. The differential diagnosis can be made by a therapeutic test. These patients do not respond to the ordinary treatment for myocardial failure, such as xanthine diuretics or digitalis, but do recover when vitamin B is administered.

Von Gierke's Disease.—This is a disorder of infants or young children, due to a disturbance of dextrose metabolism.[24, 25] The most striking feature of this disease is the enlargement of the liver, kidneys, or heart. The cause of the enlargement is the accumulation of glycogen, in abnormal amounts, in the parenchymal cells. The clinical manifestations depend upon the extent of the damage to the involved organs. Clinically, there are two types: (1) hepatic, and (2) cardiac. The number of reported cases of the cardiomegalic type of von Gierke's disease is still very few. Kato[25] found that in no case of cardiomegaly of the von Gierke type had the diagnosis been made during life. Usually this disease occurs in infants 1 year of age, or younger.

Clinically, there may be a markedly enlarged heart with progressive myocardial failure. Colds or infections often precede the onset of myocardial failure, which is manifested by rapid breathing, cyanosis, and edema. In the case reported by Antopol,[24] breathing had been unusually rapid ever since birth. There may be generalized weakness. The electrocardiographic findings in the case of Dr. White[3] were normal. A normal electrocardiogram, in addition to chemical studies, may be the means of differentiating von Gierke's disease from other types of cardiomegaly.

The diagnosis in the hepatic type has been made by biopsy of the liver. Also, in these cases one may encounter acetonuria, ketonuria, etc. "One of the most unusual features has been the failure of the adrenalin to induce an appreciable increase in blood sugar or blood lactic acid or to diminish ketonuria."[25] The blood sugar in the fasting states has been found to be low. Chemical studies should be made in all cases of cardiomegaly in children when the etiology is obscure, in order to rule out von Gierke's disease.

Post-mortem studies have helped to clarify this condition. At autopsy, it is not difficult to differentiate glycogen-storage disease from other forms of cardiomegaly. In the cardiomegalic group the size of the heart may be more than four times the normal. The enlargement is caused by marked hypertrophy. The walls of the ventricles are thickened and the ventricular cavities appear small. The myocardium is firm and thick, and on cross section appears "reddish-pink, mottled with pinkish grey."[25] The liver and kidneys may be enlarged.

On microscopic examination of the heart one finds a diffuse vacuolization of the muscle fibers. On cross section "the muscle cells appear in the form of hollow cylinders surrounded by delicately striated protoplasmic walls."[4] According to Kato,[25] "many, if not all, of the children of the cardiac group had a similarly moderate involvement of the liver and kidneys." The skeletal muscle may also be the seat of such lesions. Glycogen stains made on fresh material, properly fixed, reveal glycogen storage in the heart, liver, kidneys, or skeletal muscle in abnormal amounts. Kato[25] warns, however, that we must avoid the error of attaching too much significance to the presence of small amounts of glycogen, even in enlarged organs.

Hypertension.—Enlargement of the heart associated with hypertension, either primary or secondary, has been found in children. Hypertension following rheumatic fever[26, 27] or associated with suprarenal tumors[28] presents a definite clinical picture for differential diagnosis. In cases of spinal deformities, hypertrophy and dilatation of the heart may occur.[29, 30] In these instances the enlargement of the heart is usually right-sided, and is believed to be secondary to hypertension of the lesser circulation.

SUMMARY

The cause of enlargement of the heart in infants and young children is still a fertile field for investigation. Only in recent years has it been demonstrated that in many cases what was formerly called "idiopathic hypertrophy" of the heart was in reality associated with congenital malformations, rheumatic fever, glycogen-storage disease, myocardial degeneration and fibrosis, etc.

Eight cases of enlargement of the heart in infants and young children, presenting a definite clinical syndrome, have been described (one herein and seven in a previous paper[1]).

Cases of dilatation and hypertrophy of the heart, associated with myocardial degeneration and fibrosis, are by no means rare. They constitute the greatest number of those formerly included under the title of "idiopathic hypertrophy."[1, 5]

The differential diagnosis of the various forms of cardiomegaly has been briefly outlined.

A tentative classification of the various forms of enlargement of the heart has been suggested.

It has been emphasized that the term "congenital idiopathic hypertrophy" of the heart is not only undesirable but also confusing. In most instances the cause or nature of the enlargement of the heart in an infant or young child can be determined if the various criteria or diseases, as outlined, are kept in mind.

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BODY BUILD AND HEART SIZE

A Study of Twenty Pairs of Identical Twins and Fifteen Pairs of Unrelated Individuals With Similar Body Height and Weight

Wilfrid J. Comeau, M.D., and Paul D. White, M.D.
Boston, Mass.

THERE have been a number of clinical and anatomic studies in which various body measurements have been correlated with the size of the normal heart. Roesler,[1] in his recent text on cardiovascular roentgenology, gives an excellent, comprehensive, and critical summary of this material. It is generally agreed that, of the body measurements, body weight and body surface area give the highest degree of correlation with heart size. Body height, as a criterion, has been found to be of much less significance, while age, in the adult, has no value as a correlation factor. In view of the interest in the correlation of isolated somatic measurements with the size of the heart, it is surprising that more data are not available on heart size in individuals of similar body build.

The ideal group for such a study is, of course, identical twins. Although twins have been a source of anthropometric interest in other respects, there exists little information about the cardiovascular system other than a few general statements that the shape of the heart, the pulse rate, and the blood pressure are not infrequently quite similar in identical twins. We have found no published data which deal specifically with heart measurements in twins other than two reports in the German literature, one by von Verschuer and Zipperlen[2] and the other by Gurewitsch,[3] although Weitz,[4] without presenting measurements, does make a general statement, based on orthodiagrams, that the hearts of identical twins resemble each other very closely. Curtius (quoted by Gurewitsch) bases a similar conclusion on the size of the heart as determined by percussion. The studies of von Verschuer and Zipperlen and of Gurewitsch are not without objection, since they both made only one measurement, the transverse diameter of the heart. Furthermore, their principal interest was an evaluation of such factors as heredity, environment, and childhood diseases, on variations in the shape and size of the heart rather than an evaluation of the influence of body structure.

It seems justifiable to assume that the body build of a pair of identical twins will be much more similar than will be the case in two unrelated individuals of the same height and weight. However, in view

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of the fact that the objection might be raised that apart from body structure genetic influences per se might have a direct influence on the size of the heart, it seemed highly desirable to compare the data on twins with the data concerning a group of pairs of unrelated individuals of the same sex with similar body height and weight.

MATERIAL AND METHOD

In each instance the twenty pairs of twins were regarded as identical because of the very close similarity of their general appearance and of other gross physical characteristics. The fifteen pairs of unrelated individuals were chosen from a large group of subjects on whom determinations of heart size had been made for another purpose. These unrelated pairs were selected only on the basis of identical sex and of close similarity in body height and weight. In both groups the hearts were clinically normal and the individuals were in a good state of general health.

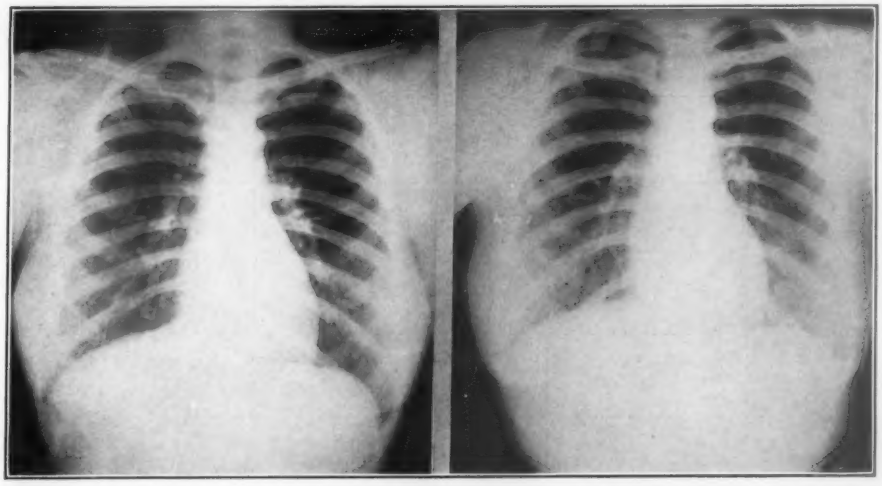

Fig. 1.—Teleoroentgenograms of identical twins (Case 13), showing the close similarity of both the size and the shape of their hearts.

Orthodiascopy was the radiographic method employed throughout this study. The frontal orthodiagram was made in the usual manner, and the standard methods were employed for determining the various measurements. A planimeter was used to compute the frontal cardiac area. The cardiac volume was estimated by the Rohrer-Kahlstorf formula, which consists of the product of the frontal cardiac area and the horizontal depth diameter of the heart in the lateral position, multiplied by the constant 0.63. We have made the subject of a recent report[5] an evaluation of this method of determining heart size. The heights of the subjects, without shoes, were measured in centimeters, and their weights in kilograms, with the heavier articles of clothing removed.

DISCUSSION

The tabulated data (Table I) show clearly that there is a striking similarity in the various heart measurements of identical twins. Of great interest are the results in the unrelated subjects (Table II), particularly when it is realized that these pairs of individuals were chosen

TABLE I

IDENTICAL TWINS

NUMBER OF PAIRS	AGE	SEX	WEIGHT (KG.)	HEIGHT (CM.)	TRANSVERSE DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	TRANSVERSE DIAMETER OF THORAX (CM.)	DIFFERENCE (CM.)	CARDIOTHORACIC RATIO (%)	DIFFERENCE (%)	LONG DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	DEPTH DIAMETER IN LATERAL VIEW (CM.)	DIFFERENCE (CM.)	FRONTAL CARDIAC AREA (SQ. CM.)	DIFFERENCE (SQ. CM.)	HEART VOLUME (C.C.)	DIFFERENCE (C.C.)
1	21	F	54 57	154 156	10.2 11.2	1.0	21.2 21.9	0.7	48 51	3	11.7 12.2	0.5	7.4 7.5	0.1	84 86	2	393 405	12
2	21	M	54½ 59	161 159	11.9 12.7	0.8	23.0 23.5	0.5	52 54	2	13.6 13.1	0.5	9.1 9.3	0.2	113 108	5	646 625	21
3	27	F	67 64	170 169	11.4 11.7	0.3	24.0 24.3	0.3	48 48	0	12.3 12.7	0.4	8.2 8.7	0.5	92 89	3	474 490	16
4	34	M	70½ 70½	179½ 179½	13.1 11.9	1.2	27.3 26.7	0.6	48 45	3	13.8 13.0	0.8	9.0 9.1	0.1	111 103	8	629 588	41
5	22	F	54½ 54	162½ 165	11.1 10.5	0.6	23.0 22.8	0.2	48 46	2	12.8 12.3	0.5	8.6 8.8	0.2	97 89	8	526 491	35
6	21	F	54 56	155 157½	10.2 11.2	1.0	20.0 23.7	3.7	51 47	4	11.2 11.5	0.3	8.2 8.9	0.7	80 83	3	414 463	49
7	21	F	51 54½	165 165	8.8 9.0	0.2	22.0 22.1	0.1	45 43	2	11.0 11.7	0.7	7.8 8.0	0.2	81 75	6	396 379	17
8	20	F	58½ 57½	164 162½	12.1 11.6	0.5	24.2 23.4	0.8	50 50	0	13.0 12.2	0.8	7.6 7.7	0.1	114 102	12	543 493	50

TABLE I—CONT'D

9	21	M	65 67	170 175	11.2 11.6	0.4	23.5 26.1	2.6	47 44	3	12.8 13.2	0.4	7.8 7.9	0.1	104 110	6	513 547	34
10	21	M	70½ 70½	179 179½	11.7 11.9	0.2	25.8 25.4	0.4	45 47	2	13.6 13.6	0	9.8 9.9	0.1	105 109	4	650 682	32
11	22	F	50 49½	161 157½	9.4 9.5	0.1	20.7 20.5	0.2	45 46	1	11.7 11.5	0.2	7.7 7.8	0.1	83 84	1	403 414	11
12	32	F	59½ 67½	165 164½	11.3 12.3	1.0	22.8 24.6	1.8	50 50	0	12.5 13.0	0.5	8.5 7.6	0.9	98 104	6	524 498	26
13	22	F	61½ 63½	160 160	10.7 11.0	0.3	23.5 23.0	0.5	46 48	2	12.3 12.7	0.4	8.5 8.2	0.3	89 90	1	476 464	12
14	19	F	59 57	167½ 167½	11.9 11.2	0.7	24.5 23.5	1.0	49 48	1	13.3 13.4	0.1	7.7 8.0	0.3	107 105	2	519 528	9
15	26	F	43½ 40½	151 150	9.4 9.4	0	20.0 20.2	0.2	47 47	0	11.4 11.5	0.1	7.3 8.1	0.8	77 84	7	356 431	75
16	19	F	57½ 60½	161 161	10.4 11.4	1.0	22.1 23.5	1.4	47 50	3	12.6 13.0	0.4	8.2 8.9	0.7	92 91	1	472 507	35
17	21	F	49½ 51	153 151½	11.3 11.4	0.1	25.0 24.0	1.0	45 48	3	12.4 12.4	0	8.5 8.2	0.3	90 92	2	483 473	10
18	35	F	64 61½	165 162½	10.7 10.4	0.3	22.3 22.0	0.3	48 47	1	12.6 12.1	0.5	8.4 8.1	0.3	94 95	1	492 482	10
19	19	F	68 64	167 167	14.0 13.6	0.4	26.5 25.5	1.0	53 53	0	14.8 13.6	1.2	9.4 9.2	0.2	124 118	6	734 681	53
20	41	F	55½ 54	167 167	10.6 10.5	0.1	23.2 24.5	1.3	46 43	3	11.1 11.7	0.6	9.1 8.7	0.4	83 86	3	478 473	5
Average						0.5		0.9		1.8		0.45		0.33		4.4		27.7

TABLE II

UNRELATED INDIVIDUALS

NUMBER OF PAIRS	AGE	SEX	WEIGHT (KG.)	HEIGHT (CM.)	TRANSVERSE DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	TRANSVERSE DIAMETER OF CHEST (CM.)	DIFFERENCE (CM.)	CARDIOTHORACIC RATIO (%)	DIFFERENCE (%)	LONG DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	DEPTH DIAMETER IN LATERAL VIEW (CM.)	DIFFERENCE (CM.)	FRONTAL CARDIAC AREA (SQ. CM.)	DIFFERENCE (SQ. CM.)	HEART VOLUME (C.C.)	DIFFERENCE (C.C.)
1	21	F	54	154	10.2		21.2		48		11.7		7.4		84		393	
	21	F	54	155	10.2	0	20.2	1.0	51	3	11.2	0.5	8.2	0.8	80	4	414	21
2	22	F	54	165	10.5		22.8		46		12.3		8.8		89		491	
	22	F	54½	165	9.0	1.5	21.1	1.7	43	3	11.7	0.6	8.0	0.8	75	14	379	112
3	34	M	70½	179½	13.1		27.3		48		13.8		9.0		111		629	
	21	M	70½	179	11.7	1.4	25.8	1.5	45	3	13.6	0.2	9.8	0.8	105	6	650	21
4	21	F	57	156	11.2		21.9		51		12.2		7.5		86		405	
	21	F	56	157½	11.2	0	23.7	1.8	47	4	11.5	0.7	8.9	1.4	83	3	463	58
5	20	F	58½	164	12.1		24.2		50		13.0		7.6		114		543	
	32	F	59½	165	11.3	0.8	22.8	1.4	50	0	12.5	0.5	8.5	0.9	98	16	524	19
6	50	F	50½	160	10.6		23.4		45		12.0		7.0		86		378	
	22	F	50	161	9.4	1.2	20.7	2.7	45	0	11.7	0.3	7.7	0.7	83	3	403	25

TABLE II—CONT'D

7	48 35	F F	63½ 64	165 165	11.5 10.7	0.8	20.7 22.4	1.7	51 48	3	12.4 12.6	0.2	7.6 8.4	0.8	89 95	6	426 482	56
8	45 45	M M	71 71	163½ 163½	11.6 12.2	0.6	26.1 23.0	3.1	44 53	9	12.4 12.3	0.1	10.3 11.1	0.8	87 99	12	566 694	128
9	21 34	M M	70½ 70½	179½ 179½	11.9 13.1	1.2	25.4 27.3	1.9	47 48	1	13.6 13.8	0.2	9.9 9.0	0.9	109 111	2	682 629	53
10	45 43	M M	70½ 71½	169½ 168½	12.2 12.7	0.5	25.0 25.0	0	49 51	2	12.4 13.5	1.1	9.6 8.4	1.2	97 113	16	587 599	12
11	37 22	F F	50 50	162½ 161	10.4 9.4	1.0	21.8 20.7	1.1	43 45	2	12.4 11.7	0.7	8.1 7.7	0.4	78 83	5	395 403	8
12	17 21	F F	54 54	159 160	10.1 10.3	0.2	22.8 21.8	1.0	49 47	2	11.5 13.0	1.5	7.3 8.2	0.9	81 98	17	372 505	133
13	21 21	M M	64 64	176 176	11.5 12.5	1.0	26.0 25.3	0.7	44 49	5	14.3 14.3	0	8.8 8.5	0.3	122 119	3	674 634	40
14	22 40	M M	67 67½	168 169½	12.9 13.1	0.2	25.9 28.5	2.6	50 46	4	12.9 13.2	0.3	9.5 9.7	0.2	101 115	14	602 700	98
15	44 45	M M	63½ 62	172 172½	13.2 11.1	2.1	24.3 27.0	2.7	54 41	13	14.5 12.7	1.8	9.4 9.2	0.2	117 97	20	690 563	127
Average						0.83		1.7		3.6		0.58		0.74		9.4		60.7

only on the basis of corresponding height, weight, and sex. Table III summarizes the significant data given in Tables I and II.

As pointed out above, in spite of similar height and weight, the general body build in unrelated individuals will vary considerably more than in identical twins, due to constitutional and racial differences in body structure. In this connection it is interesting to note that the greatest variation in the measurements occurred in the internal diameter of the thorax in the unrelated individuals. This is taken to indicate that in this group there actually existed a definite and appreciable difference in body build of the pairs in spite of similar height and weight. Considering this factor we feel that even the heart size of these pairs of unrelated individuals showed an amazing degree of similarity.

TABLE III

AVERAGE OF DIFFERENCES BETWEEN CARDIAC MEASUREMENTS OF PAIRS OF IDENTICAL TWINS AND PAIRS OF UNRELATED INDIVIDUALS OF THE SAME SEX WITH SIMILAR BODY HEIGHT AND WEIGHT

SUBJECTS	TRANSVERSE DIAMETER OF HEART (CM.)	TRANSVERSE DIAMETER OF CHEST (CM.)	CARDIOTHORACIC RATIO (%)	LONG DIAMETER OF HEART (CM.)	DEPTH DIAMETER OF HEART (CM.)	FRONTAL AREA (SQ. CM.)	HEART VOLUME (C.C.)
Identical twins	0.5	0.9	2	0.5	0.3	4	28
Unrelated individuals	0.8	1.7	4	0.6	0.7	9	61

We feel justified, therefore, in concluding that, although individual somatic measurements correlate to a varying degree with heart size, the highest degree of correlation will be found when the various body measurements are considered in the composite form of body build. Further, we believe that the influence of genetic, racial, and environmental factors on the heart is principally through their effect on body structure, of which all organs, including the heart, are integral parts.

SUMMARY AND CONCLUSIONS

1. The heart size as determined by several orthodiascopic measurements was investigated in twenty pairs of identical twins and in fifteen pairs of unrelated individuals of the same sex with similar body height and weight.

2. The data show a close correspondence of heart size in the identical twins. In the pairs of unrelated individuals the similarity in the heart measurements, although less marked, is rather close, particularly when constitutional and racial differences in body structure which are not brought out by height and weight alone are considered.

3. The conclusion is reached that heart size in normal individuals is dependent principally on body build, and that genetic, racial, and environmental factors are usually important chiefly as they affect body structure. The combination of height and weight, although the best index of body build which exists at present, is not completely satisfactory. We hope that anthrometric studies may produce a more reliable index for expressing body build and thereby offer a more satisfactory measurement to correlate with heart size.

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Department of Clinical Reports

THROMBOANGIITIS OBLITERANS IN A DIABETIC

WILLIAM S. COLLENS, M.D., AND NATHAN D. WILENSKY, M.D.
BROOKLYN, N. Y.

WE HAVE had occasion to observe that clinicians frequently loosely employ the term "endarteritis" to describe most cases of obliterative peripheral arterial disease. Because of this laxity in terminology, the peripheral circulatory impairment in diabetes has often been called "endarteritis obliterans."

We are prompted to present this report in order to stress the importance of greater clarity and accuracy in the clinical differentiation of organic obliterative disease of inflammatory and degenerative or arteriosclerotic origin. It must be remembered that the term "endarteritis" should signify the existence of an inflammatory process in the intima of an artery. The most common inflammatory disease encountered is thromboangiitis obliterans. Other conditions that produce arteritis are tuberculosis, syphilis, pneumonia, rheumatic fever, typhus fever, typhoid fever, and periarteritis nodosa.

The outstanding type of arterial impairment which occurs in diabetes is the degenerative form known as arteriosclerosis obliterans. Its earmarks are degenerative changes in the intima and the media, which assume a fairly definite pattern. Winternitz and his co-workers[1] have recently published a most significant monograph on this subject. They present evidence to show that the degenerative lesion which eventuates in the reduction of the lumen of a major artery arises from hemorrhage from the vasa vasorum into the intima or media. This hemorrhage is then followed by a reaction characterized by an increase in the vascularity of the wall of the vessel, hyaline degeneration in the area of the hemorrhage and, finally, fibrosis and calcification. A cross-sectional study of the artery will usually show the pathologic changes just described, with so much thickening of the wall of the vessel as to encroach upon the lumen.

The presence of thromboangiitis obliterans as a causative factor in impairment of arterial flow in diabetes is an extremely rare phenomenon. A search of the literature has disclosed three reports, including only six cases, of which four can be accepted as authentic.[2, 3, 4] In order to establish beyond question a diagnosis of thromboangiitis obliterans in a diabetic, it is necessary to possess clinical data which are pathognomonic or, better still, histologic evidence. The presence of peripheral cir-

From the Diabetic Clinic and Department of Medicine, Israel Zion Hospital.
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culatory impairment in a diabetic usually means arteriosclerosis unless proved otherwise.

We have just encountered a case of a diabetic with peripheral vascular disease and gangrene of a foot in which histologic study of the arteries disclosed the existence of thromboangiitis obliterans. The extreme rarity of the combination of diseases prompts us to present this case.

CASE REPORT

S. I., 42 years of age, an Italian Jew and a rabbi by profession, first came under observation Sept. 23, 1937. He complained of burning pain in both feet for a period of five years. He also had intermittent claudication which had become progressively worse, so that at the time of admission to the hospital he experienced a cramp in his calf muscles on walking 200 feet. He also complained of rest pain and found some relief by hanging his legs over the side of the bed. During this five-year period he had been treated with hypertonic salt solution intravenously and diathermy and had ceased smoking. He had formerly smoked thirty-five cigarettes a day.

Examination on admission disclosed evidence of marked impairment of the blood supply of both legs, worse on the right than the left. No pulsations were palpable in the dorsalis pedis, posterior tibial, and popliteal arteries of the right leg. The left dorsalis pedis pulsation was feeble. There was a small ulcer on the dorsal surface of the right small toe. The Buerger test was positive, more so on the right than the left.

Oscillometric readings were as follows: Above knee—right, 0, left, ½; below knee—right, 0, left, trace; at ankle—right, 0, left, 0; dorsalis pedis—right, 0, left, 0.

The venous filling time[5] was fifty seconds in the right foot and thirty-four seconds in the left.

During his stay in the hospital it was discovered that the patient had diabetes. On one occasion the sugar content of the urine was 4 per cent. His fasting blood sugar was 238 mg. per cent. The nonprotein nitrogen content of the blood was normal. The blood Wassermann reaction was negative. The blood pressure was 170/110. Roentgenologic studies of his extremities failed to disclose any calcification of his arteries. The electrocardiogram showed left axis deviation and was otherwise normal. The glucose tolerance test disclosed a typical diabetic curve.

These findings were indicative of extensive interruption in peripheral arterial flow, more especially in the right leg. Clinically, one was justified in making a diagnosis of arteriosclerosis obliterans. The absence of calcium deposits, as shown roentgenologically, left the diagnosis somewhat in doubt, for such extensive circulatory impairment is almost always accompanied by such deposits in the walls of the arteries. His diabetes was adequately controlled with a diet containing 250 gm. of available glucose, together with 30 units of insulin daily. Local conservative therapy failed to relieve the patient of pain and the gangrenous ulcer became progressively larger. He left the hospital Oct. 25, 1937, and was admitted to the St. Luke's Hospital November 23, where a mid-thigh amputation of his right leg was performed. The operative wound healed by primary union. The following are the microscopic findings, which Dr. Leila Knox, the pathologist, was kind enough to send us.

"Sections through the popliteal artery show the medial coat free of calcification and only a little sclerotic. Some new blood vessels penetrate throughout the muscle. Occupying the lumen and attached to the intimal coat is a large amount of hyaline thrombus. One portion of its base is invaded by giant cells of the foreign-body type, some containing fat droplets, fibroblasts, and mononuclear cells. Other areas show the lumen completely obliterated by old hyalinized connective

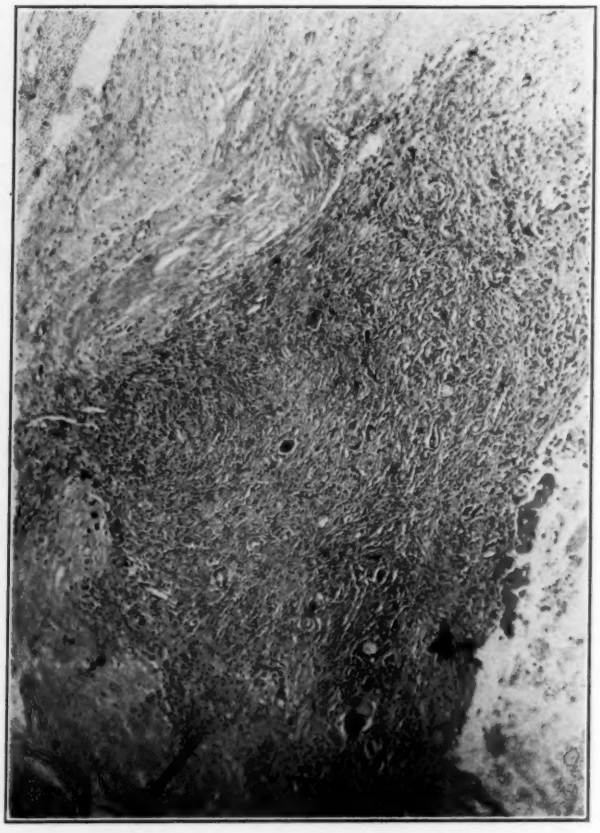

Fig. 1.—Section of popliteal artery showing inflammatory infiltration of intima. Hyaline degeneration and fibrosis of intima are seen in the upper left-hand portion of the photograph (magnification ×125).

tissue and a few recanalized vessels. Portions of the fibrous tissue contain calcium salts. Sections of the anterior and posterior tibial and dorsalis pedis arteries show the lumen free and their walls for the most part very slightly altered. Rarely a vessel shows some calcium infiltration in its media. Some of the nerve fibers show degenerative changes with round cell infiltration (Figs. 1 and 2).

"The diagnosis, based upon the histologic study, is thromboangiitis obliterans."

DISCUSSION

A clinical diagnosis of thromboangiitis obliterans can be made only in the presence of certain adequate criteria, which include evidence of peripheral circulatory impairment in an adult under the age of 40 years, a history of migrating phlebitis, and the absence of calcification of the vessels. It is not absolutely essential that migrating phlebitis be present. Its association with the disease, however, is pathognomonic of thromboangiitis obliterans. On the other hand, if the patient is a diabetic past the age of 40 years, if hypertension is present and there are calcium deposits in the arterial walls, the diagnosis of arteriosclerosis obliterans cannot be doubted.

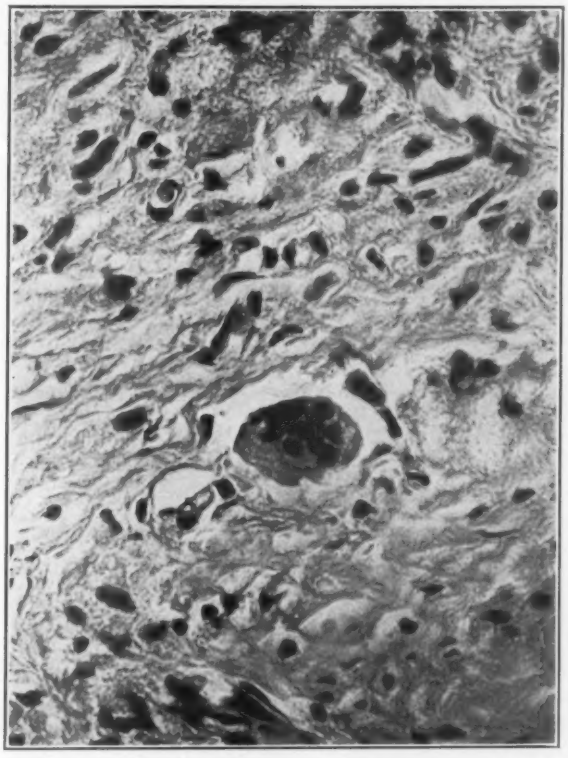

Fig. 2.—High-power view of inflammatory lesion showing foreign body giant cell, fibroblasts, and mononuclear cells (magnification ×800).

In the case which we have reported an absolute diagnosis could not be made on the clinical manifestations alone. Although the patient was a diabetic and had hypertension, the fact that his peripheral arteries could not be visualized roentgenologically and that the arterial blood supply of his legs had been impaired since he was 37 years of age suggested that the peripheral vascular disorder was not of arteriosclerotic origin. It remained for the histologic examination of his major vessels to finally establish the fact that in addition to a mild degree of arteriosclerosis the patient suffered from thromboangiitis obliterans.

SUMMARY

A case of thromboangiitis obliterans in a diabetic is reported. This is a very rare occurrence.

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COARCTATION OF THE AORTA WITH ASSOCIATED STENOSIS OF THE RIGHT SUBCLAVIAN ARTERY

WILLIAM S. LOVE, JR., M.D., AND JOSEPH H. HOLMS, M.D.
BALTIMORE, MD.

KING[1] has recently reviewed the blood pressure readings in 170 reported cases of coaretation of the aorta, and has added five more cases to the literature of this subject. There were only ten cases in which a significant disparity of pressure in the two arms was present, and, of these ten patients, nine had a higher pressure in the right arm than in the left, possibly due to involvement of the isthmus of the aorta and the mouth of the left subclavian in the same fibrotic anomaly—an explanation offered by Parkes-Weber and Knop,[2] who quote D. E. Bedford's description of such an instance. East[3] reported one case in which the blood pressure in the left arm was found to be 195/145 and that in the right arm, 135/100. No autopsy examination of this patient was made. However, in a second case, upon which clinical observations were not available, autopsy revealed stenosis of the isthmus of the aorta and an anomalous origin of the right subclavian which might have resulted in interference to the circulation of the right arm. He suggests that some such anomaly as this might have been the explanation of the lower blood pressure observed in the right arm in the first case. We wish to report the following case, in which the same type of inequality of the pressures in the two arms was present, and for which peculiarity an adequate cause was discovered.

REPORT OF CASE

A colored man, 44 years old, was admitted to one of the hospitals of Baltimore, Oct. 17, 1932. He complained of a sore throat and an ulcer in the roof of the mouth. Water came through his nose whenever he drank. There had been a penile lesion at the age of 18 years, and the patient admitted having had three or four gonorrheal infections. There were no subjective symptoms of cardiovascular disease.

Physical examination revealed a well-developed and well-nourished colored man. The pupils reacted normally. There was a perforating ulcer of the posterior portion of the hard palate; it entered the left nasal cavity. Several small lymph nodes were palpable in the left posterior triangle of the neck. No abnormalities were noted on examination of the lungs. Marked pulsation of the left carotid, and pulsation both above and below the left clavicle, were readily detected. There was a strong pulsation in the suprasternal notch, and the examining physician felt that there was a mass at this location. The heart was reported to be enlarged to the left, and a loud systolic murmur was heard over the entire precordium,

From the Department of Medicine, University of Maryland.
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but was maximal at the apex. The pulse rate was 92 and the pulse was said to be noticeably stronger in the left arm. The blood pressure was 210/95 in the left arm, and 150/90 in the right arm. Other findings were essentially negative. A diagnosis of probable syphilitic ulceration of the hard palate and aneurysm of the aorta was made.

Nothing is known of this patient's subsequent course until he was readmitted to the same hospital and died there of bronchopneumonia in June, 1935. The diagnosis was changed to carcinoma of the hard palate during this admission.

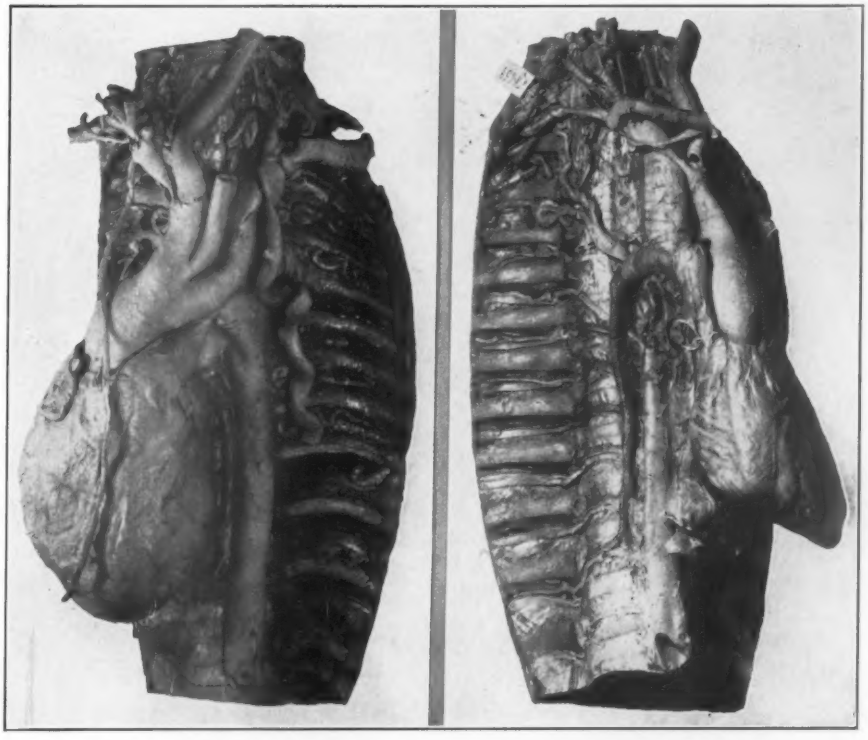

Fig. 1. Fig. 2.

Fig. 1.—The heart has been moved to the right. The innominate and left common carotid arteries arise from a short trunk. The right subclavian artery is markedly stenosed at its point of origin. The right internal mammary artery is placed across the heart so that it may be compared with the very much larger and more tortuous artery on the left. The ligamentum arteriosum is readily seen extending from the pulmonic artery to the stenosis at the isthmus of the aorta. There is a knoblike dilatation of the aorta just distal to the coarctation. The dilated and tortuous left intercostal arteries are striking, and there has been considerable erosion of the ribs.

Fig. 2.—In this view the heart has been reflected to the left. A single large arterial trunk arising from the aorta below the site of coarctation courses upward and to the right, and in this illustration appears from behind the azygos vein. From this artery arise the second, third, and fourth right intercostals. The second intercostal anastomoses with the right superior intercostal, and two other anastomosing branches arise from the anomalous trunk. The arterial flow to the right subclavian distal to the point of stenosis takes place through these channels. The right intercostals are only slightly dilated and tortuous from the fourth down. The artery (*X*) seen looping in front of the vertebrae is a tortuous branch of the left thyreocervical trunk which anastomoses with the second intercostal on the left.

No autopsy was obtained. However, the body was assigned to the Anatomy Department of the University of Maryland, where one of us was asked to see it because of an anomalous aorta. The above history was then obtained.

Description of Specimen.—The anatomical findings to which we especially wish to call attention were as follows: The left common carotid and the innominate

arteries took origin from a common trunk. The right subclavian arose from the innominate and at its point of origin was not wider than several millimeters. It reached its maximum width at the vicinity of the origin of the inferior thyroid and internal mammary arteries and the cervico-acromial trunk. A large artery, arising from the arch of the aorta, gave origin to the second, third, and fourth intercostals on the right. The second intercostal anastomosed with the right superior intercostal, which was a branch of the costocervical artery; this last vessel arose from the subclavian distal to the point of stenosis. Doubtless the greater part of the arterial flow to the subclavian artery distal to the stenosis took place through this channel. On the right side all of the arteries that customarily play a role in the collateral circulation of isthmic stenosis were much smaller than those on the left.

Fig. 3.—This illustration displays the extreme tortuosity of the left intercostal arteries, and the resulting erosion and notching of the ribs. The origin of the innominate and left common carotid arteries from a short trunk is shown. This anomaly doubtless was responsible for the clinical impression of a pulsating mass below the suprasternal notch.

Coarctation of the aorta was obvious, and there was a knoblike dilatation of the thoracic aorta just below the site of stenosis. The tremendously dilated and tortuous intercostals, internal mammary, and other vessels playing a role in the

collateral circulation on the left side were striking. Except for the anomalies described above, the collateral circulation developed in this case did not differ in any important detail from that which usually occurs in coarctation of the aorta.

CONCLUSION

We have described a case of coarctation of the aorta in which the very unusual finding of a much lower blood pressure in the right arm than in the left was present. An associated stenosis of the right subclavian artery offered an adequate explanation for this clinical observation. So far as we have been able to ascertain, this is the first case of this type reported in the literature.

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Department of Reviews and Abstracts

Selected Abstracts

Fry, William E., and Swanson, Edward E.: Digitalis Assay by the Cat Method Under "Sodium Amytal" Anesthesia. J. Am. Pharm. A. **28**: 309, 1938.

As anesthetics, in the assay of digitalis by the cat method, two short-acting barbituric acid derivatives were compared with ether.

When the cats were anesthetized with the barbituric acid compounds, it required more digitalis to kill than with ether.

The size of the cat unit for digitalis varies with the anesthetic agent used.

AUTHORS.

Johnson, J. Raymond, and Di Palma, Joseph R.: Intramyocardial Pressure and Its Relations to Aortic Blood Pressure. Am. J. Physiol. **125**: 234, 1939.

A method of optical recording is described for measuring directly the extent of the intramyocardial pressure at any desired depth in the wall of the left ventricle, and the contour of such pressure curves is described. By means of simultaneous records of the pressure from the ventricular wall and from the aorta the following important relations are found to obtain:

1. During the height of systole there exists in the wall of the ventricle a gradient of pressure decreasing from the deeper to the more superficial layers.
2. In the depth of the myocardium this pressure is always greater than aortic pressure but in the superficial layers it may be equal to or even less than the pressure in the aorta and coronary arteries.

These results indicate that while the deeper coronary vessels must become completely occluded during the height of cardiac contraction there may be a continuous forward movement of blood in the more superficial layers of the myocardium.

AUTHORS.

Brüner, H., and Mertens, W.: Experimental Changes in Blood Volume I. Blood Pressure and Pulse Rate Following Bleeding. Arch. f. Kreislaufforsch. **3**: 223, 1938.

Studies were carried out on twenty-four dogs in whom acute hemorrhages were produced. The effect of hemorrhage was compared in some animals before and after denervating the reflex buffer nerve mechanism (carotid sinus and aortic end organ areas). The buffering nerve mechanism was found able to cope, as far as blood pressure is concerned, with a loss of as much as 20 per cent of the blood volume. With each further loss of blood up to 40 per cent of the blood volume, the effect on blood pressure became greater. Beyond 40 per cent the further loss of blood had less effect on blood pressure. The lowest point attained by the blood pressure is 35 to 45. The pulse rate increases progressively with hemorrhage and reaches its maximum when the blood pressure reaches its lowest level.

In the animal with denervated buffer nerve mechanisms, the blood pressure fall is progressive in successive hemorrhages and reaches its low point of 35 to 45. The initially rapid heart rate is not changed significantly.

The amount of blood which can be lost before the nerve buffering mechanism fails is dependent on the initial blood pressure.

KATZ.

Eckey, P., and Vorwerk, W.: The Effect of Strophanthin on the Gaseous Metabolism and Heart Minute Volume in the Presence and in the Absence of Buffer Receptors. Arch. f. Kreislaufforsch. 3: 235, 1938.

Fifteen dogs were used and anesthetized with urethane. The effect of intravenous strophanthin was observed before and after denervating the buffer receptors (carotid sinus and aortic areas). In animals with the buffer nerves intact, the minute volume decreases following strophanthin. At the same time the oxygen consumption and blood pressure were unchanged. In animals with the buffer receptors denervated, the minute volume of the heart, the blood pressure and the oxygen consumption increased.

On the basis of these results, the authors postulate the possibility that the difference in action of strophanthin in normal and failing hearts might be due to a loss of buffering nerve receptor activity.

KATZ.

Meyer, F.: A Manometer With Photoelectric Registration (Air Bubble Manometer). Ztschr. f. Kreislaufforsch. 30: 734, 1938.

A blood pressure manometer is described briefly. This consists of a horizontal tube with a gas bubble in it so situated as to be interposed between a light source and a photoelectric cell. The size of the gas bubble varies with the pressure in the manometer and so alters the amount of light permitted through. This is recorded by the photoelectric cell. When calibrated, the pressure values can be determined.

KATZ.

Griffith, J. O., Zinn, C. J., and Comroe, B. I.: Effect of Sympathectomy on the Vasa Vasorum of the Rat. Arch. Path. 26: 984, 1938.

While it may be assumed that the vasa vasorum share in the general response of blood vessels to sympathectomy, this has never been demonstrated. By injecting particulate matter into the circulation of rats in which bilateral lumbar sympathectomy had been performed and into normal rats, the authors have found that the number of vasa vasorum in the femoral artery of the rat is increased five days after lumbar sympathectomy.

NAIDE.

Cottenot, P., and Heim de Balsac, R.: Experimental Anatomical-Radiological Study of the Circulatory System of the Normal Newborn Infant by Post-Mortem Shadows. Gynéc. et obst. 35: 251, 1938.

Post-mortem injections of the various chambers of the heart in eight stillborn children, showed the position of the ventricles relatively more anterior in relation to the auricles than in the adult. The whole heart is more globular and larger in proportion to the thorax. The left auricle (lying posteriorly) and the right ventricle (lying anteriorly) have relatively small volume; this is explained by the inactive state of the pulmonary circulation. For the same reason the pulmonary vessels also are poorly developed. The aortic arch is entirely to the front and to the left of the midline, and the ascending and descending limbs of the arch are seen side by side rather than behind each other. The trunk of the pulmonary

artery is in striking contrast to the branches which are quite small, while the trunk is continuous with the ductus arteriosus. This creates an x-ray shadow very similar to that of persistent ductus arteriosus in the adult.

JENSEN.

Burch, George E., and Sodeman, William A.: A Direct Method for the Determination of Venous Pressure; Relationship of Tissue Pressure to Venous Pressure. J. Clin. Investigation **18**: 31, 1939.

The application of the tissue pressure apparatus to the direct determination of venous pressure was highly satisfactory and disclosed definite advantages.

Comparison of indirect and direct determinations of venous pressure on the same vessel indicates that the former are in error by approximately the tissue pressure. This factor becomes increasingly important as the venous pressure decreases.

AUTHORS.

Hollmann, H. E., and Hollmann, W.: The Einthoven Triangle Compared With Other Lead Combinations. Arch. f. Kreislaufforsch. 3: 191, 1938.

The first section deals with the mathematical and graphic solution of Einthoven's formulations. It is restated that formula Lead II = Lead I + Lead III applies to any triangle, not only to the equilateral one. As for the geometric aspects of the Einthoven triangle, there are definite limits in applying it actually because of eccentricity of the heart and nonhomogeneity of the body field.

In the second section the author used four schemes to get the vectorgram (record of the resultant vector during the heart cycle inscribed as a standing wave on a cathode ray oscillograph), two of which are rather elaborate; the others were chest triangle and the limb triangle respectively. These were all similar.

KATZ.

Grosse, F.: Electrocardiographic Findings in Cardiac Infarctions With Various Chest Leads. Arch. f. Kreislaufforsch. 3: 245, 1938.

This is a study based on nineteen patients, of whom sixteen had anterior, eight had posterior, and five had combined anterior and posterior infarcts. The author correlated clinical and electrocardiographic findings. The value of chest leads is emphasized especially when the limb leads are atypical. An M-shaped QRS and an elevated S-T segment were found at autopsy to have occurred in a patient with combined infarction. In determining prognosis the clinical and not the electrocardiographic findings are important.

KATZ.

Levy, Robert L., Bruenn, Howard G., and Russell, Nelson G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency. Am. J. M. Sc. **197**: 241, 1939.

A method has been described for inducing generalized anoxemia without rebreathing: employing an apparatus which enables the subject to breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen at the normal rate of pulmonary ventilation.

Changes in the form of the electrocardiogram have been analyzed following the induction of anoxemia in 105 persons, comprising 66 normals, 23 with disease of the coronary arteries, 11 in whom coronary disease was suspected but doubtful, and 5 with severe anemia.

Criteria for normal and abnormal responses have been evolved. It is recognized that the material is relatively small and that the criteria must be regarded as tentative. It has not been possible, thus far, to correlate the clinical diagnoses with the anatomic lesions.

Changes regarded as abnormal have occurred in patients with clinical symptoms and signs of coronary insufficiency. Similar alterations have been observed in those with anemia but without signs of cardiac disease.

There have been no serious untoward effects. Because of two unpleasant reactions, it is suggested that the test should not be given to patients with cardiac insufficiency and should not be repeated in the same patient within twenty-four hours.

Changes in the form of the electrocardiogram caused by induced anoxemia may be used as a clinical test for insufficiency of the coronary circulation, whether this be manifest or latent. An index is afforded of the adequacy of the "coronary reserve." It should be of value in distinguishing pain of coronary origin from pain in the chest due to other causes, as well as from pain referred from the abdomen. It is possible that it can be employed also to study, in man, the effect of drugs and of various surgical procedures on the efficiency of the coronary blood flow. Such studies are in progress.

AUTHORS.

Masshoff, W.: Influence of Diphtheria on the Size of the Heart and on the Heart Muscle Structure. Arch. f. Kreislaufforsch. 3: 142, 1938.

This study gives a post-mortem analysis of twenty hearts from patients 1½ to 16 years of age, dying of diphtheria or its complications. Every heart showed an enlargement in one of its chambers. Evidence indicates that heart failure was right sided in these patients, and there was evidence of myocardial degeneration rather uniformly distributed throughout the heart. Inflammatory damage in the heart appears to be a complication.

KATZ.

Lepeschkin, E.: The Normal Chest Electrocardiogram in Childhood. Arch. f. Kreislaufforsch. 3: 321, 1938.

This is a study based on fifty normal children of from 2 weeks to 15 years of age utilizing ten to twenty roentgen-controlled combinations of chest electrodes and left leg or right arm electrodes.

The initial complex is diphasic. In infants the first upright phase is larger than the inverted phase on the right of the sternum. In older children this is true over the apex. The difference is attributed to the relative thickness of the two ventricles at these two ages. The T wave is inverted on the right chest anteriorly and upright on the left. On transition a diphasic T is found. This transition is more to the left anteriorly in children than in grown-ups and this deviation from the midline is greater the younger the child. These differences are related to the more lateral position of the interventricular groove, in the younger child. These changes are considered in relation with the regional distribution of the activity.

KATZ.

Keil, Harry: The Rheumatic Subcutaneous Nodules and Simulating Lesions. Medicine 17: 261, 1938.

Consideration of the data presented in this monograph seems to point in the direction of the establishment of the following principles:

The term rheumatic nodule should be applied to those lesions occurring in the course of undoubted rheumatic fever. The lesion presents definite characteristics,

the most important being the location, the transiency (relative and absolute), and the relations to the other rheumatic phenomena, notably cardiac involvement. The highest degree of clinical specificity is enjoyed in childhood, and the rheumatic subcutaneous nodule may be said to be highly specific of rheumatic fever in that age group, provided the clinical attributes correspond closely with those mentioned in the text.

The specificity of the rheumatic nodule is dependent on its clinical properties and relations. The combination of pathologic changes found in microscopic examinations, while often suggestive, shows no pathognomonic characteristics and may be simulated by other lesions.

The true rheumatic nodule is practically always associated with clinical evidence of cardiac involvement in one form or another. The evidence compiled in this monograph substantiates the view that disease of the heart is the fundamental hall-mark of rheumatic fever. This may not always be evident clinically, but its occurrence is to be expected at post-mortem examination. When evidence of cardiac involvement in one form or another is completely lacking at necropsy, there is reason to believe that the case was not one of rheumatic fever and the burden of proof rests on those who wish to classify the condition in the rheumatic category. On the other hand, the presence of rheumatic heart disease, particularly if the changes are old and healed, does not necessarily indicate that nodules appearing at the time are inevitably related to the rheumatic process; each case must, therefore, be evaluated critically, and the factor of coincidence must be taken into account. The difficulties inherent in this problem are increased, owing to the lack of uniformity in the pathologic criteria for the recognition of rheumatic fever.

The typical nodule in rheumatoid arthritis differs from that in rheumatic fever in many clinical attributes and in some pathologic respects. The clinical differences appear to be more important than the pathologic differences, the latter still requiring evaluation.

The nodule in rheumatoid arthritis shows greater resemblances to the juxta-articular node in syphilis. This is especially true in a clinical sense and it probably also holds pathologically, if the ordinary methods of staining are used for microscopic study. On the other hand, it is possible that investigations pursued by supravital staining (McEwen) may furnish data of differential diagnostic importance.

The conception of the syphilitic nodule as an entity rests on three features: (1) its association with other manifestations of syphilis; (2) the almost invariable presence of a positive Wassermann reaction; (3) the striking response to anti-syphilitic remedies.

The controversy regarding the relative incidence of subcutaneous lesions in rheumatoid arthritis and in syphilis is clarified by the realization that both varieties of nodules occur, but that their respective incidence will be governed largely by the type of material under observation.

The pathologic criteria for the diagnosis of a "rheumatic nodule" are discussed critically. Evidence is presented to show that these appearances, as observed in the ordinary microscopic examinations, are not pathognomonic of a single disease. How far the supravital studies will provide criteria for the differentiation of the various nodules is still problematic, but it is a method worthy of extended investigation. Caution is advised in drawing etiologic conclusions on the basis of morphologic resemblances.

AUTHOR.

Hadfield, G.: The Rheumatic Lung. Lancet 2: 710, 1938.

The primary lesion responsible for the consolidation of the "rheumatic lung" is widespread fibrinous alveolitis. This is followed by a cellular infiltration, mono-

nuclear in type, relatively slow in development but eventually becoming copious and diffuse.

In fatal cases this primary lesion is complicated by hyaline pseudomembrane formation in most of the alveolar ducts in the consolidated lung.

As in other varieties of pneumonitis this process takes place in lungs in which the finest ramifications of the airway contain viscid albuminous exudate and after a period of severe inspiratory dyspnea.

The dyspnea which initiates membrane production in the rheumatic lung is probably primarily cardiac in origin.

AUTHOR.

Goormaghtigh, Norbert, and Handovsky, Hans: Effect of Vitamin D_2 (Calciferol) on the Dog. Arch. Path. **26**: 1144, 1938.

The authors have made extensive pathologic and pharmacologic studies, extending over a period of three years, of the effect of calciferol (vitamin D_2) on the dog. Observations were centered on the arterioles of the kidney. Moderate daily doses of calciferol caused hypertrophy and morphologic changes indicative of increased cell metabolism in both types of cells in the arteriolar media (the ordinary smooth muscle and the afibrillar cell). The afibrillar cells are identical with the cells found in the glomi or arteriovenous shunts in the skin. Larger but nonlethal doses do not affect the afibrillar cells but cause regressive changes in the smooth muscle cells. Some of these changes are reversible after discontinuation of the treatment. These regressive changes are present to a smaller extent in the arterioles of the spleen, neurohypophysis, thyroid, gonads, adrenal and pancreas. In the normal dog calciferol leaves the aorta macroscopically unchanged. With the dosage employed, alterations of the elastic membrane or intimal reactions are rarely observed. Arteriolar calcinosis is absent. Calciferol in heavy doses causes necrosis of the arteriolar media, a lesion similar to that found in scarlet fever and eclampsia.

In the dog's kidney calciferol causes arteriolonecrosis, with or without nephritis, depending on the dose employed. They offer the following explanation of the pathogenesis of the renal lesion. In hypervitaminized dogs tubular lesions are produced as a result of the profound changes in the chemical make-up of the blood, with marked excretion of calcium. Because of the anatomic connection between the vascular pole of the glomerulus and distal part of the distal convoluted tubule, damage to the tubule causes mechanical irritation of the vas afferens, with vasoconstriction of the arteriole. This vasoconstriction results in glomerular collapse or regression. They stress therefore the significance of the tubular lesions in nephrosclerosis, pointing out that these lesions are responsible for glomerular regression.

Doses of from 50 to 70 micrograms per kilogram cause inversion of the vascular response to epinephrine. Heavier doses increase the sensitivity of the hypertensive response.

Arterial hypertension develops when the treatment is maintained at a dosage of from 100 to 700 micrograms per kilogram per day. Doses not exceeding 250 micrograms per kilogram have a thyrotropic effect.

The significance of these observations in the problem of human arteriosclerosis is discussed.

NAIDE.

Steinert, R.: Hypertension. Does the Mortality Increase in Essential Hypertension? A Statistical Analysis. Ztschr. f. Kreislaufforsch. **30**: 693, 1938.

This is an analysis of causes of death of people over 50 from 1925 to 1934. On the basis of the assumption that most cases of apoplectic death are brought about

by essential hypertension, the author concludes that in Norway no increase occurred in the latter in this ten year period since the death rate from apoplexy was unchanged (41/10,000 population). By contrast, death from chronic heart disease 48 per cent in the last five-year period as compared with the first.

KATZ.

Pickering, G. W.: The Problem of High Blood Pressure in Man. Brit. M. J. 1: 1, 1939.

The Herzstein Lectures were delivered before the University of California and Stanford University, San Francisco, May 23 to 26, 1938.

The author attempts to develop a line of thought rather than to prove a scientific hypothesis. He discusses the available evidence supporting the theory of a chemical substance formed in the kidney which, when liberated, is fixed in the blood vessels and results in a rise in blood pressure.

MCCULLOCH.

Horton, Bayard T.: The Outlook in Thrombo-Angiitis Obliterans. J. A. M. A. 111: 2184, 1938.

This is a review of 948 patients with thromboangiitis obliterans. The distribution as to geography, age, sex, and race is discussed. Twenty-one of the patients were women; the remaining 927 were men.

Ninety-three per cent of the total were smokers. A greater percentage of amputations occurred among the smokers than among the nonsmokers.

A study of amputations for periods of three, five, and ten years after the onset of the disease indicates that approximately 70 per cent of patients will go for a period of three years from the onset without the necessity of amputation, whereas only 60 per cent will go for a period of five years and only 40 per cent for a period of ten years without being obliged to undergo amputation.

Early diagnosis and thorough education of the patient concerning the nature of his disease and the care of his extremities are important in preventing amputation.

NAIDE.

Mills, John H., and Horton, Bayard T.: Clinical Aspects of Aneurysm. Arch. Int. Med. 62: 949, 1938.

A total of 596 cases of aneurysm were recorded at the Mayo Clinic in the years 1925 to 1935, inclusive. In this series of cases, 143 of the aneurysms were intracranial, 339 were intrathoracic, 80 were intra-abdominal, 21 involved the extremities, and 13 were of a miscellaneous character. The etiology, symptoms, and physical findings of the various types of aneurysms encountered are discussed. Syphilis was present in 3.5 per cent of the cases of intracranial aneurysm, in 70 per cent of the cases of thoracic aneurysm, in 8.8 per cent of the cases of intra-abdominal aneurysm, in 9.5 per cent of the cases of aneurysm of an extremity, and in 7.7 per cent of the miscellaneous cases of aneurysm. In a total of 172, or 28.9 per cent, of the 596 cases, the diagnosis of aneurysm was verified at operation or necropsy.

NAIDE.

Goldbloom, A. Allen, and Lieberson, Abraham: Clinical Studies in Circulatory Adjustments. Am. J. M. Sc. 197: 182, 1939.

The factors maintaining circulatory equilibrium, cardiac output, blood volume, venous pressure, blood pressure, and circulation time are defined and discussed.

Historically the importance of cardiodynamic studies in explaining the nature of, and circulatory mechanisms involved in certain clinical conditions; hypertension, central versus peripheral failure, right versus left heart failure, hyperthyroidism, and polycythemia is stressed.

It has been found useful from the diagnostic and therapeutic points of view to group decompensated cardiacs into plus and minus forms of failure, based on blood volume readings.

From the practical viewpoint, the greatest uses made of cardiodynamic studies are in the following:

1. Borderline cases of hyperthyroidism, where an increased cardiac output, increased blood volume and rapid circulation time distinguish this condition from neurocirculatory asthenia or incipient tuberculosis (in which the above values are normal).

2. In polycythemia vera the very high blood volume and hematocrit reading are usually sufficient to distinguish it from the symptomatic polycythemias, which do not yield such high figures.

3. In the differentiation between right and left heart failure, aside from clinical differences, the lengthened arm-to-lung circulation time in right-sided failure is of distinct value. By subtracting the arm-to-lung circulation time from the total pulmonary circulation time (arm-to-head) one can estimate the speed through the left heart circuit.

4. In decompensation, often the very first sign of right heart failure is an increase in the venous pressure.

AUTHORS.

Davis, D.: The Role of Rest and Exercise in Congestive Heart Failure. New England J. Med. **219**: 412, 1938.

There is no agreement in the literature as to the length of time patients should rest after evidence of congestive failure has disappeared, or as to the advisability of exercise in convalescence. The historical aspect of these questions is considered.

The question of the advisability of exercise in convalescence is discussed at length. No data were found to support the contention that this therapy improves the capacity of the heart.

The results of prolonged bed rest in eleven cases are compared with those in a control group treated in the accepted manner. The course in these eleven cases was appreciably better than that in the control group.

These results call for a program which will take into consideration an adequate initial period of rest, adequate subsequent reduction in activity, and periodic prophylactic bed rest. Such a program is outlined.

AUTHOR.

Wolferth, Charles C., and Margolies, Alexander: Movements of Roentgen-Opaque Deposits in Heart Valve Areas. Am. J. M. Sc. **197**: 197, 1939.

A cardiac roentgenkymogram timed by an electrocardiogram was made in such a way as to demonstrate the movements, toward and away from each other, of the apex and of a calcium deposit in the region of the aortic valve. From the data obtained in this case and four others (three previously published) in which roentgenkymograms were made of calcium deposits in either the mitral valve or aortic valve area, the following points are emphasized.

The change in size and shape of the left ventricle during contraction is probably due more to shortening of the long axis than to movement of the lateral wall.

The floor of the auricle (roof of the ventricle) does not remain in a relatively fixed position as is usually assumed, but is pulled vigorously toward the apex during ventricular systole, while the apex is moving toward the base. The directions of movement are reversed in diastole.

The movements of the left ventricular border are much smaller than the movements of base and apex. The shortening of the long axis may be so great that the left border actually moves outward during the early part of systole. The foregoing facts should be taken into consideration in any attempt to study ventricular contraction by means of recording the movements of the left ventricular wall. These movements may fail to reflect the vigor or extent of the left ventricular contraction.

The marked movement of the auricular floor, as a result of ventricular contraction, must create a powerful suction which is an important factor in bringing about auricular filling.

It is probable that when movements of the external walls of the heart are restricted, the filling and emptying of its chambers are made possible by the effects of ventricular contraction and relaxation on movement of the tissues separating auricles and ventricles.

AUTHOR.

Reid, Mont R., and McGuire, Johnson: Arteriovenous Aneurysms. Ann. Surg. **108:** 643, 1938.

An analysis of twenty-one cases of arteriovenous and nine cases of cirsoid aneurysms is presented, which is supplemented by observations upon experimentally produced arteriovenous aneurysms in dogs.

Sixteen of the arteriovenous aneurysms were operated upon and all of them, except one case of pulsating exophthalmos, were cured. In two instances the aneurysms healed spontaneously without operation. Four patients failed to return for later operations and could never be traced. All of the nine cirsoid aneurysms were operated upon; three were cured, and the other six were more or less improved. There were no deaths in the entire series of thirty cases. There was a total of thirty-nine operations upon the twenty-four patients who were subjected to surgical treatment.

Clinical and experimental observations which may throw some light upon the physiologic and pathologic effects of arteriovenous fistulas are discussed in some detail. The principal effects noted and studied were: ten instances of cardiac damage; eleven instances of thinning and dilatation of the proximal artery; circulation time upon six patients; blood volume upon three patients; ten instances of Branham's bradycardic phenomenon; thirteen instances of blood pressure alterations; studies upon the venous blood pressures of nine patients; nine instances of markedly increased collateral circulation; five instances of an increase in the size and length of an extremity; four instances of associated nerve paralyses; two instances of double arteriovenous fistulas; and two instances of spontaneous healing of the aneurysm.

In our limited clinical and experimental observations, we could not confirm Holman's findings of a marked increase of the total circulating blood.

A Venturi meter was used in some of the experiments to measure the flow of blood in a segment of the vena cava. An easy method of making an arteriovenous fistula which can be alternately closed and opened is illustrated.

The time to operate, and the standard curative operative procedures, are discussed. Two new operative procedures are illustrated and described in the case reports.

AUTHORS.

Heumans, C.: Some Aspects of Blood Pressure Regulation and Experimental Arterial Hypertension. Surgery 4: 487, 1938.

Experimental investigations have demonstrated that the regulation of blood pressure is essentially and fundamentally an automatic, proprioceptive reflex mechanism. In fact, the endovascular pressure itself regulates automatically the cardiac output, the circulating blood volume, and the peripheral vascular resistance so well that the arterial pressure is maintained within or quickly restored to normal limits. This homeostasis of the arterial pressure is effected mainly by the intermediation of the pressoreceptor innervation of different arterial and venous vascular areas.

The author's experiments suggest that the arterial hypertension induced by renal ischemia may be due to a humoral factor which increases the excitability of the peripheral blood vessels to constrictor stimulations, mainly to the neurogenic vasoconstrictor influences, the same humoral factor inducing, on the other hand, a direct peripheral vasoconstriction and a disturbance in the physiologic mechanisms of the pressoreceptive reflex regulation of blood pressure. The sympathectomy up to the total removal of both ganglionic chains neither prevents nor cures this experimental nephrogenic hypertension.

AUTHOR.

Craig, W. McK.: Essential Hypertension: The Selection of Cases and Results Obtained by Subdiaphragmatic Extensive Sympathectomy. Surgery 4: 502, 1938.

The surgical treatment of hypertension, which consists of subdiaphragmatic resection of the major, minor, and lesser splanchnic nerves, celiac ganglion, and lumbar sympathetic ganglions, is associated with a small risk and is followed by satisfactory alleviation of symptoms in selected cases.

Assuming that all hypertension can be divided into four groups, depending upon the severity, Group 1 does not require surgical treatment and Group 4 is too severe and too far advanced to warrant the expectation of adequate results. Groups 2 and 3 then should be considered for operative treatment. More important than the group are the preoperative tests which indicate the potential physiologic changes that will follow sympathetic denervation of the vascular area below the diaphragm.

The so-called test indicates the upper limits of the blood pressure resulting from emotion or cold. The four other tests indicate the lower limits of the blood pressure readings associated with prolonged vasodilatation, and, therefore, denote the probable values for the blood pressure following extensive sympathectomy. They are as follows: (1) Twenty-four consecutive hourly determinations of the blood pressure are made while the patient is in bed, to establish the maximal blood pressure, the minimal blood pressure, and the mean or average blood pressure. (2) Slow and intermittent intravenous injection of a 5 per cent solution of pentothal sodium is made until there is no further drop in blood pressure. (3) One-half grain (0.032 gm.) of sodium nitrite is administered at intervals of thirty minutes until six doses have been given. (4) Hourly determinations of blood pressure are made during rest and sleep for a minimum of twenty-four hours.

If the blood pressure drops to nearly normal and if the patient is less than 50 years of age, the operation should be considered.

The results in a large series of cases have been quite satisfactory. The effect of the operation is physiologic in character, and, if so considered, the results justify the procedure.

AUTHOR.

American Heart Association, Inc.

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50 WEST 50TH STREET, NEW YORK, N. Y.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

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